Biology 5357: Chemistry & Physics of Biomolecules
Fall 2023

Lecture 3: Membrane Structure & Mechanics

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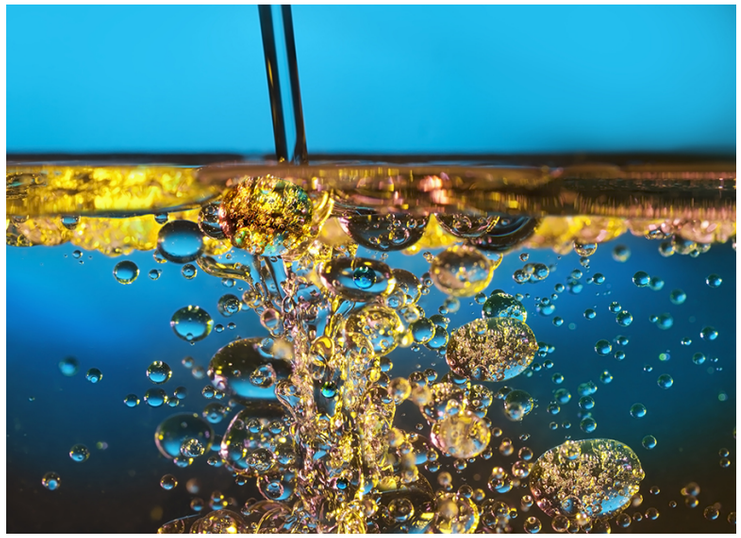
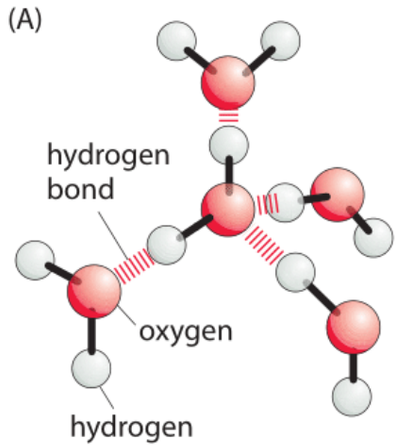
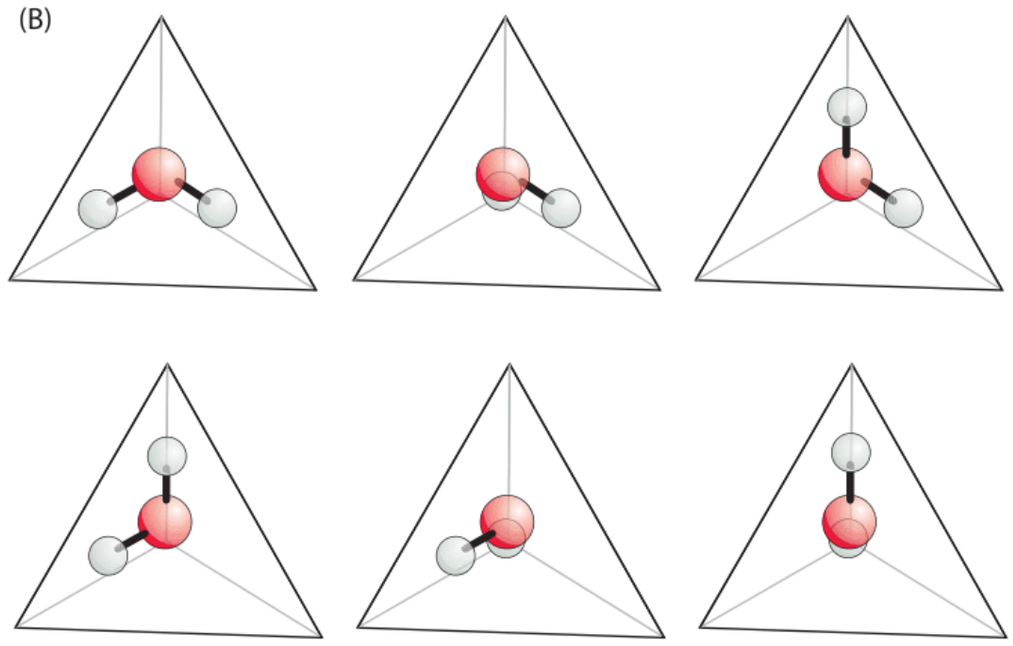
Reading for this week:

Phillips, R. (2018). **Physics of Biological Membranes** https://dx.doi.org/10.1007/978-3-030-00630-3_3

The hydrophobic effect







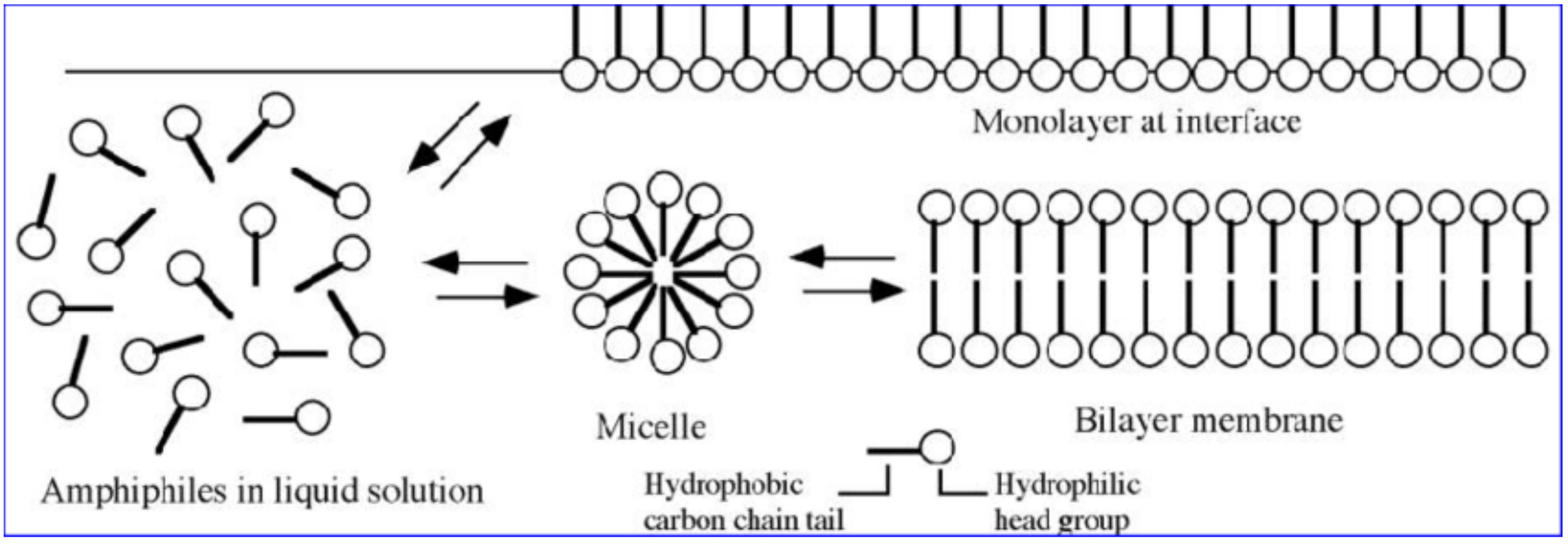
Adapted from Ken Dill, molecular driving forces. http://book.bionumbers.org/what-is-the-energy-scale-associated-with-the-hydrophobic-effect/

- Water forms a network of hydrogen bonds with itself
- The number of hydrogen bonds can be described in a simplified tetrahedral network, showing 6 possible configurations of the central water molecule making a hydrogen bond with a neighbor
- Changing one of these water molecules to a non-polar molecule that does not form hydrogen bonds reduces the number of states to 3, just a single face of the triangle
- Loss of entropy yields 0.42 kcal/mole for each water position replaced
- Each methylene group adds 0.8 kcal/mole to the hydrophobic effect
- Drives association of non-polar molecules to reduce the water accessible surface area

Self-assembly of amphiphiles

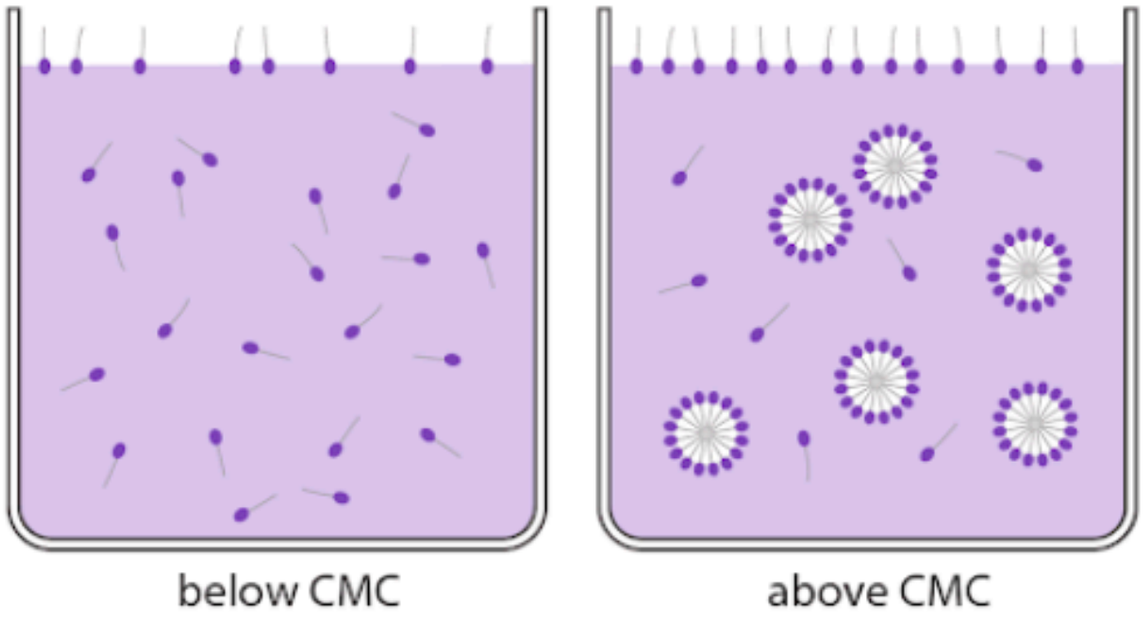
Chain entropy

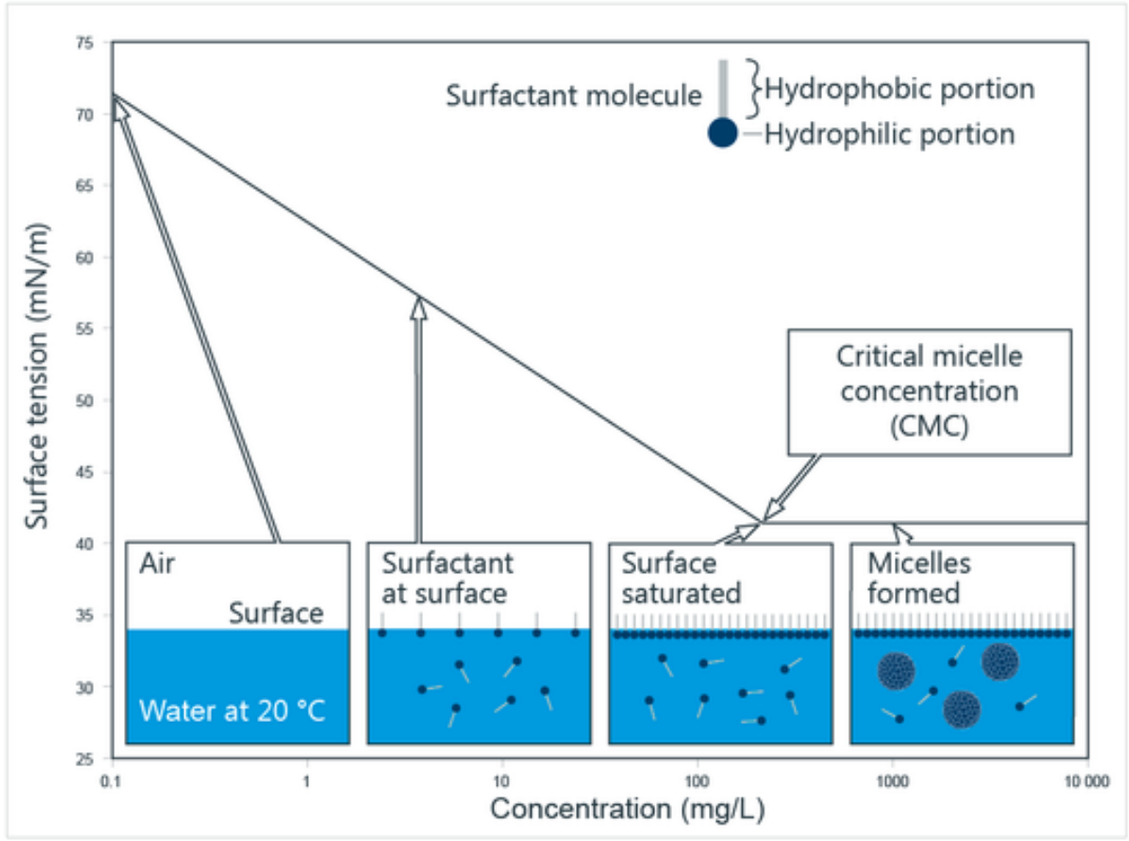
Intermolecular interactions
(VDW, H-Bonds, Elec.)

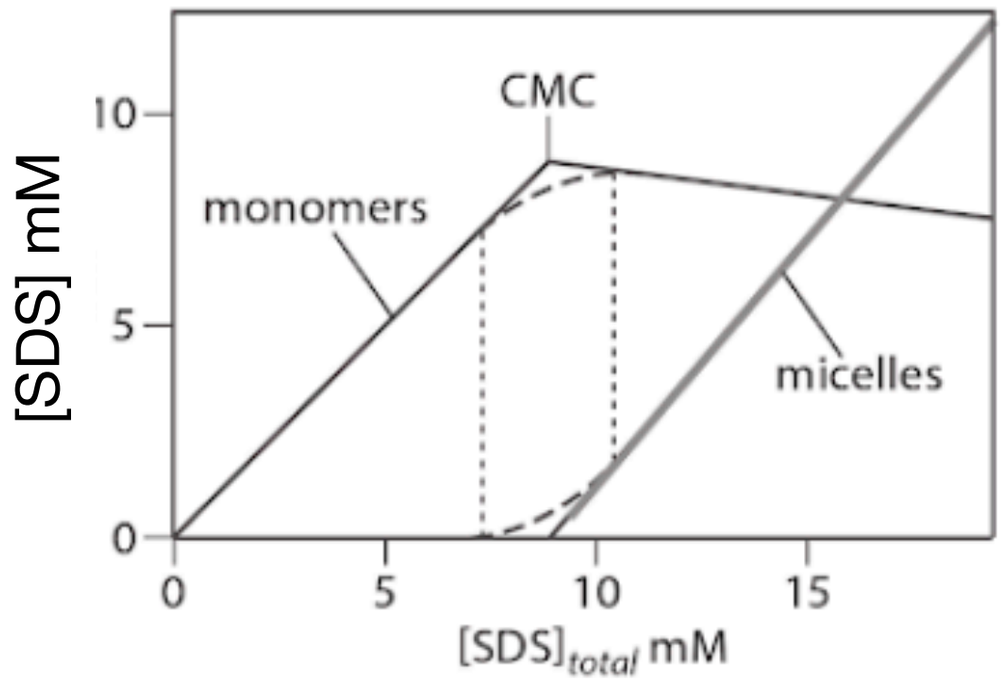


The Critical Micelle Concentration (CMC)

Figure from “Cell Membranes” by Lukas Buehler

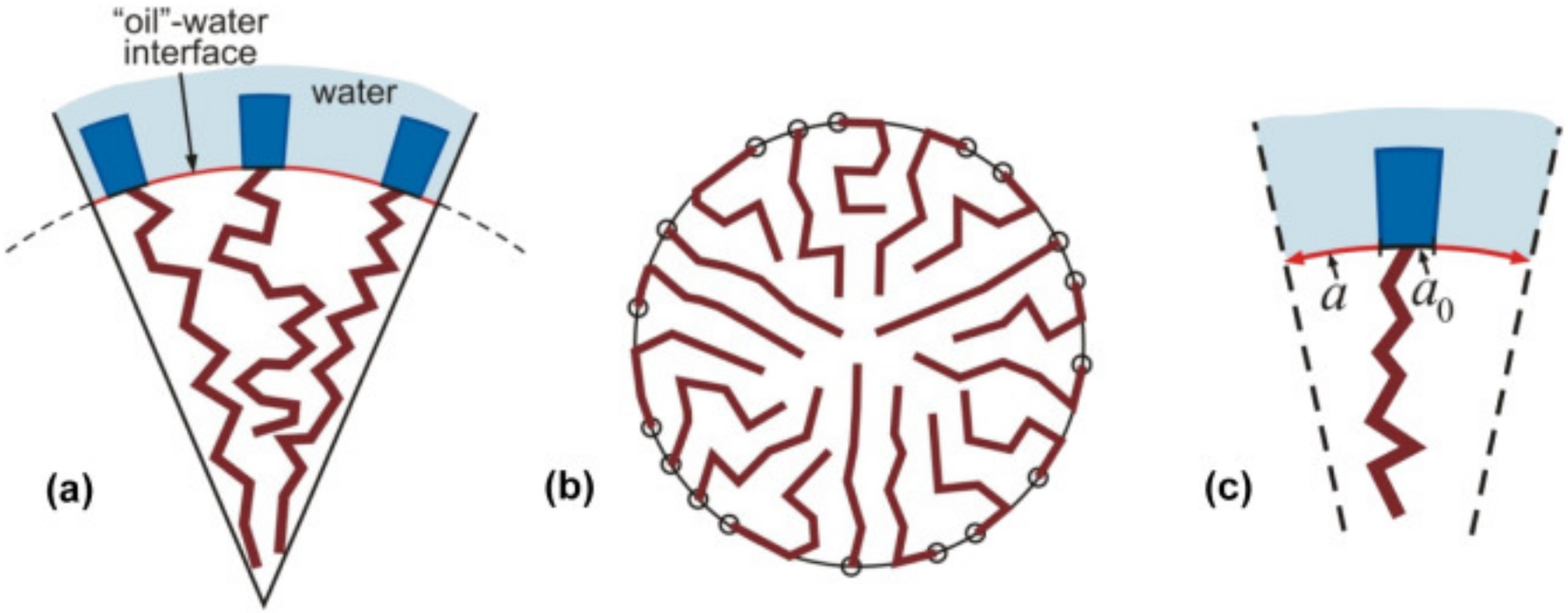






What defines the CMC?

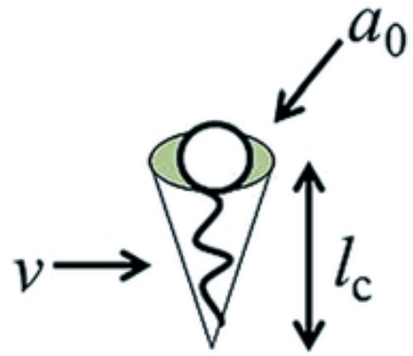
Danov et al., 2018



- **Structure of hydrophobic group:** increase in carbon chain increases micellar size, decreases CMC
- **Increase in hydrophilic head group:** increases hydrophilicity and increases CMC
- **Addition of electrolytes** for ionic surfactants decrease CMC and increase micellar size due to a reduction in head group repulsion
- **Temperature**: mainly affects nonionic surfactants, increases in temperature up to the cloud point increase micellar size and decrease CMC
- **Concentration**: aggregation number in micelle can change above CMC making non-spherical micelle structures

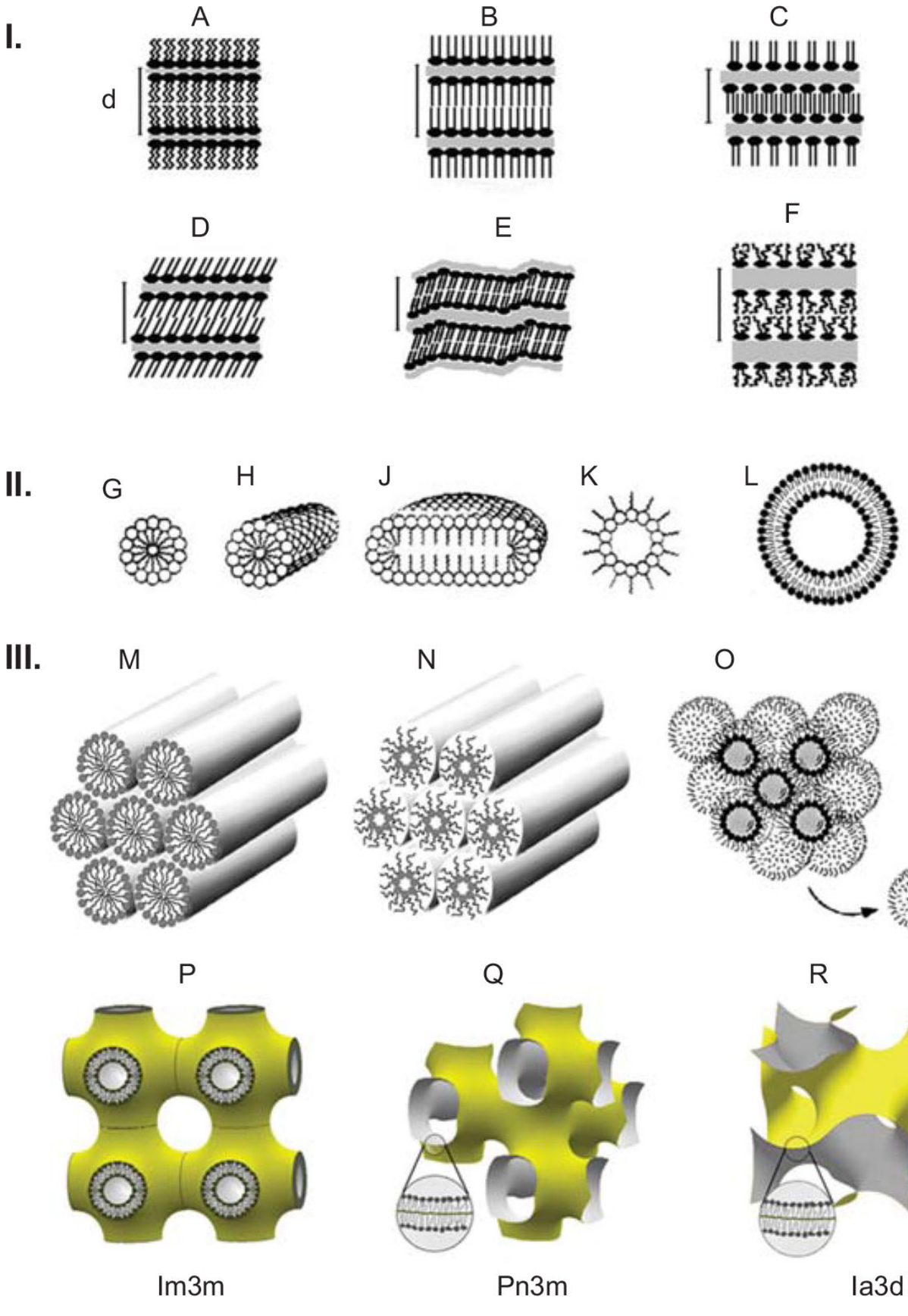
CMCs of detergents

Detergent	MW	CMC
CHAPS	614.88	8 mM
CHAPSO	630.88	8 mM
BIGCHAP	878.06	2.9 mM
DeoxyBIGCHAP	862.06	1.4 mM
Octylglucoside	292.37	25 mM
Heptylthioglucoside	294.41	30 mM
Octylthioglucoside	308.44	9 mM
Decylmaltoside	482.57	1.8 mM
Dodecylmaltoside	510.62	0.17 mM
Nonylthiomaltoside	484.60	2.4 mM
MEGA-8	321.41	-
MEGA-9	335.44	25 mM
MEGA-10	349.46	7 mM
Sucrose monocholate	732.85	4.7 mM
Sodium cholate	448.57	14 mM



$$\text{CPP} = v/a_0 l_c$$

Critical Packing Parameter ($v/a_0 l_c$)	Critical Packing Shape	Structures Formed
< 1/3	Cone	Spherical micelles
1/3 – 1/2	Truncated cone	Cylindrical micelles
1/2 -1	Truncated cone	Flexible bilayers, vesicles
~1	Cylinder	Planar bilayers
>1	Inverted truncated cone or wedge	Inverted micelles



Structures of lipid phases.

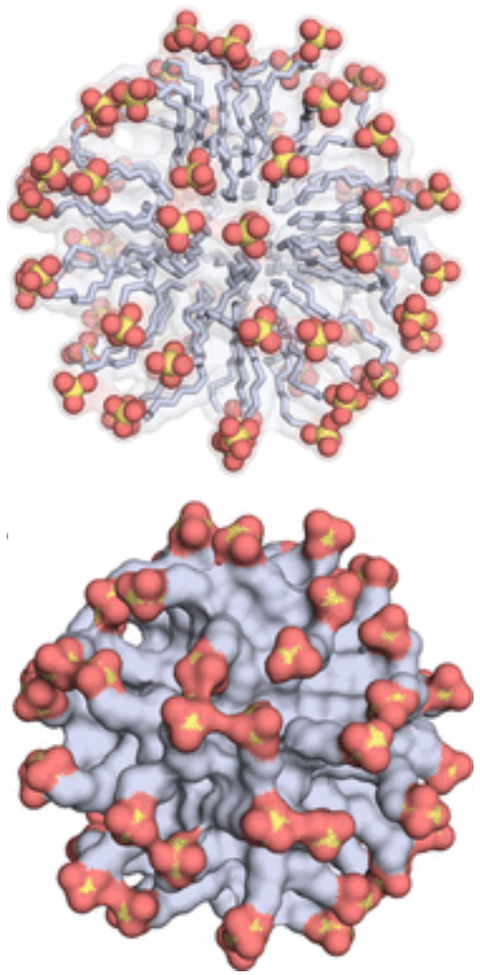
I. Lamellar phases: (A) subgel, L_c; (B) gel, L_β; (C) interdigitated gel, $L_\beta^{[int]}$; (D) gel, tilted chains, L_β'; (E) rippled gel, P_β'; (F) liquid crystalline, L_α .

II. Micellar aggregates; (G) spherical micelles, M_I; (H) cylindrical micelles (tubules); (J) disks; (K) inverted micelles, M_{II}; (L) liposome;

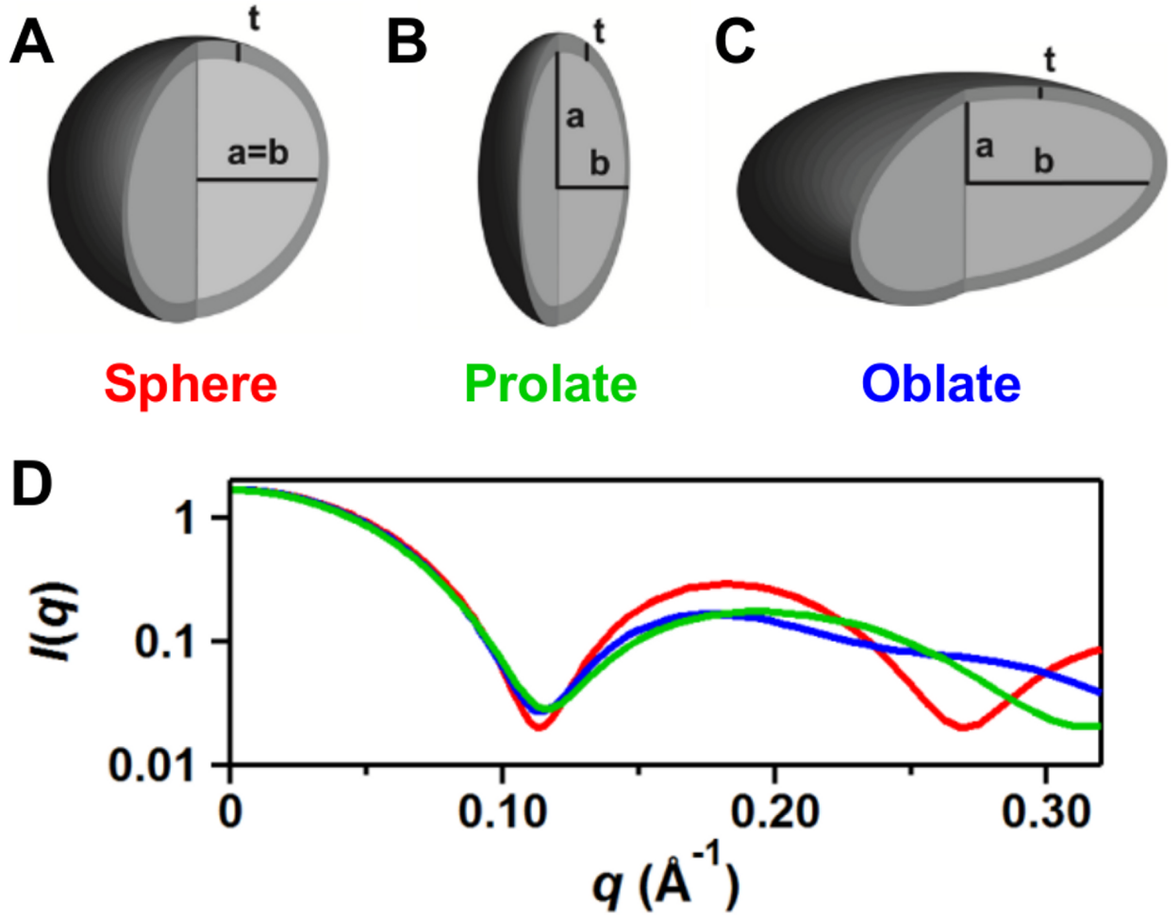
III. Non-lamellar liquid-crystalline phases of various topology; (M) hexagonal phase H_I; (N) inverted hexagonal phase H_{II}; (O) inverted micellar cubic phase $Q_{II}^{[M]}$; (P) bilayer cubic (Q_{II}) phase Im3m; (Q) bilayer cubic phase Pn3m; (R) bilayer cubic phase Ia3d.

From Koynova R, Tenchov B. Transitions between lamellar and non-lamellar phases in membrane lipids and their physiological roles. OA Biochemistry 2013 Apr 01;1(1):9.

Structure of detergent micelles



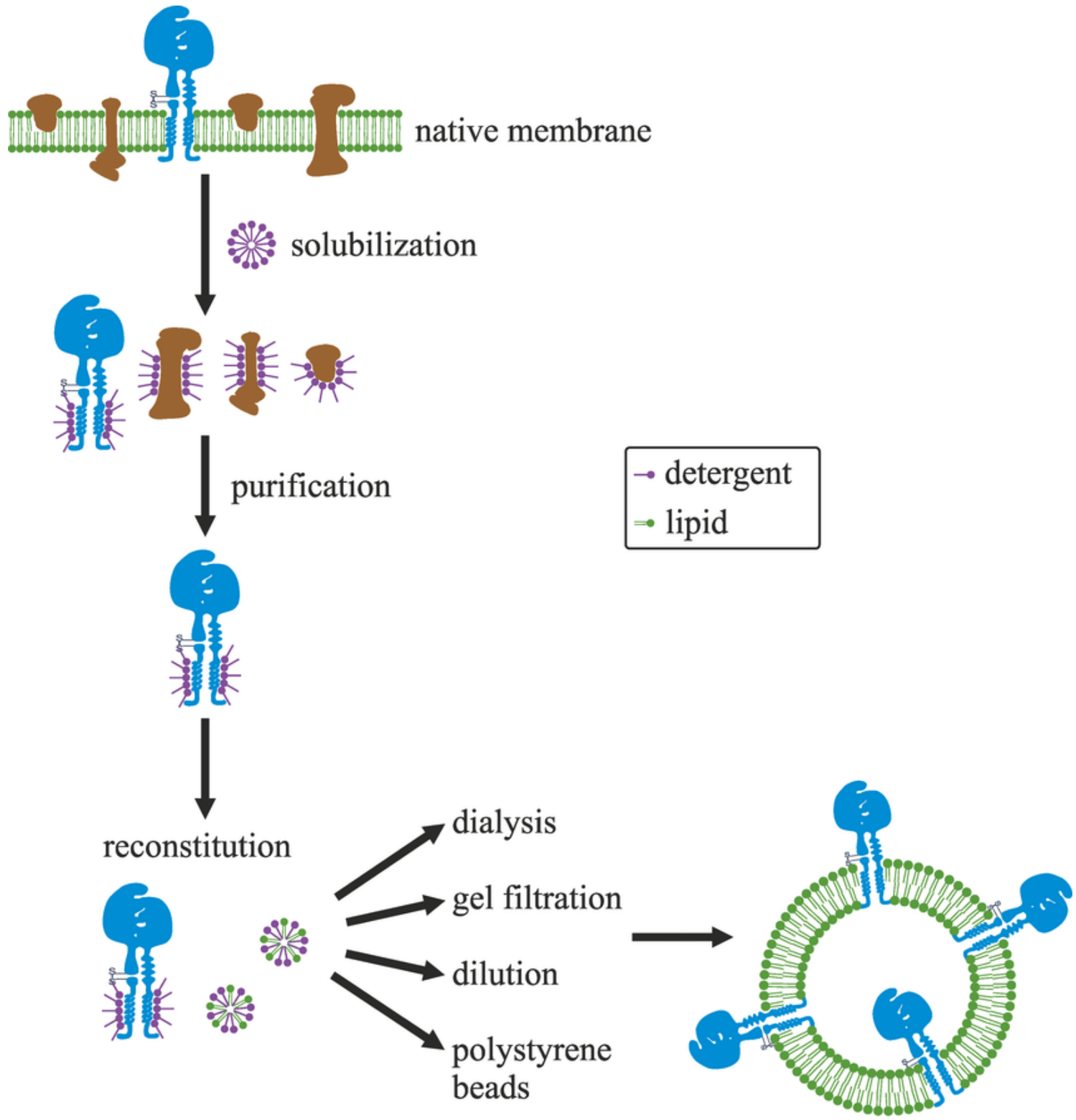
ACS Omega 2017, 2, 8, 4524-4530



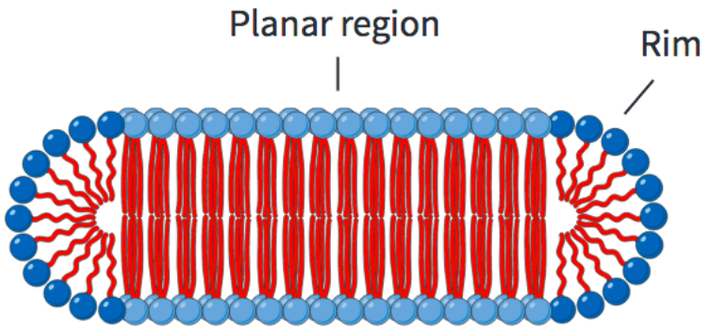
Oliver RC, Lipfert J, Fox DA, Lo RH, Doniach S, Columbus L (2013) Dependence of Micelle Size and Shape on Detergent Alkyl Chain Length and Head Group. PLoS ONE 8(5): e62488. https://doi.org/10.1371/journal.pone.0062488

R - radius
Nagg - aggregation number

Purifying membrane proteins

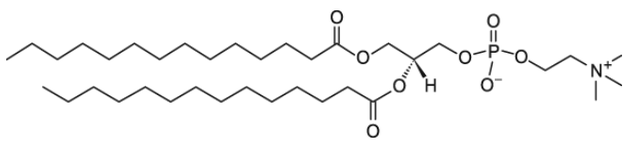


Mixtures of detergent & lipids - bicelles

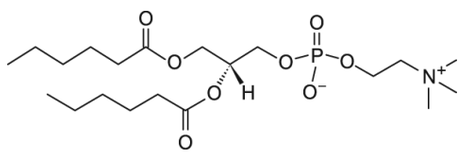


Schema of bicelle structure

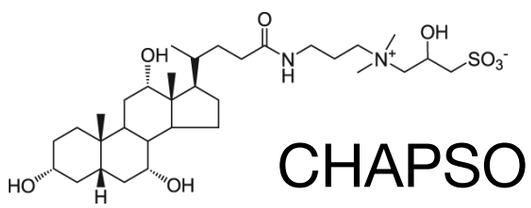
DMPC

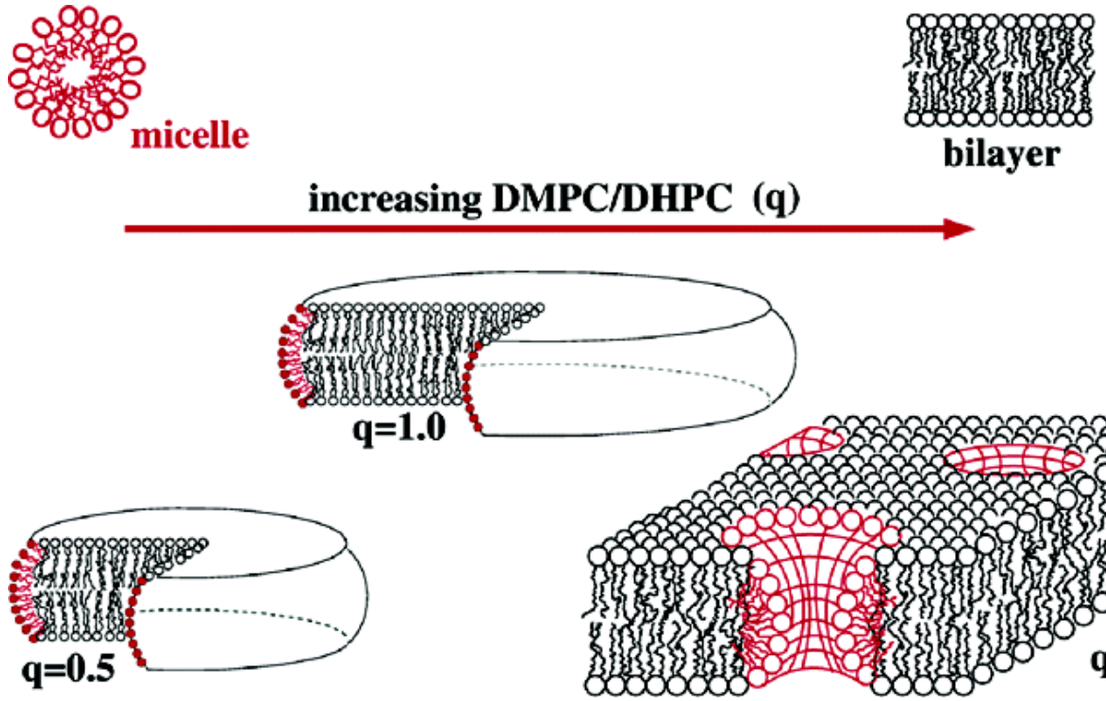


DHPC



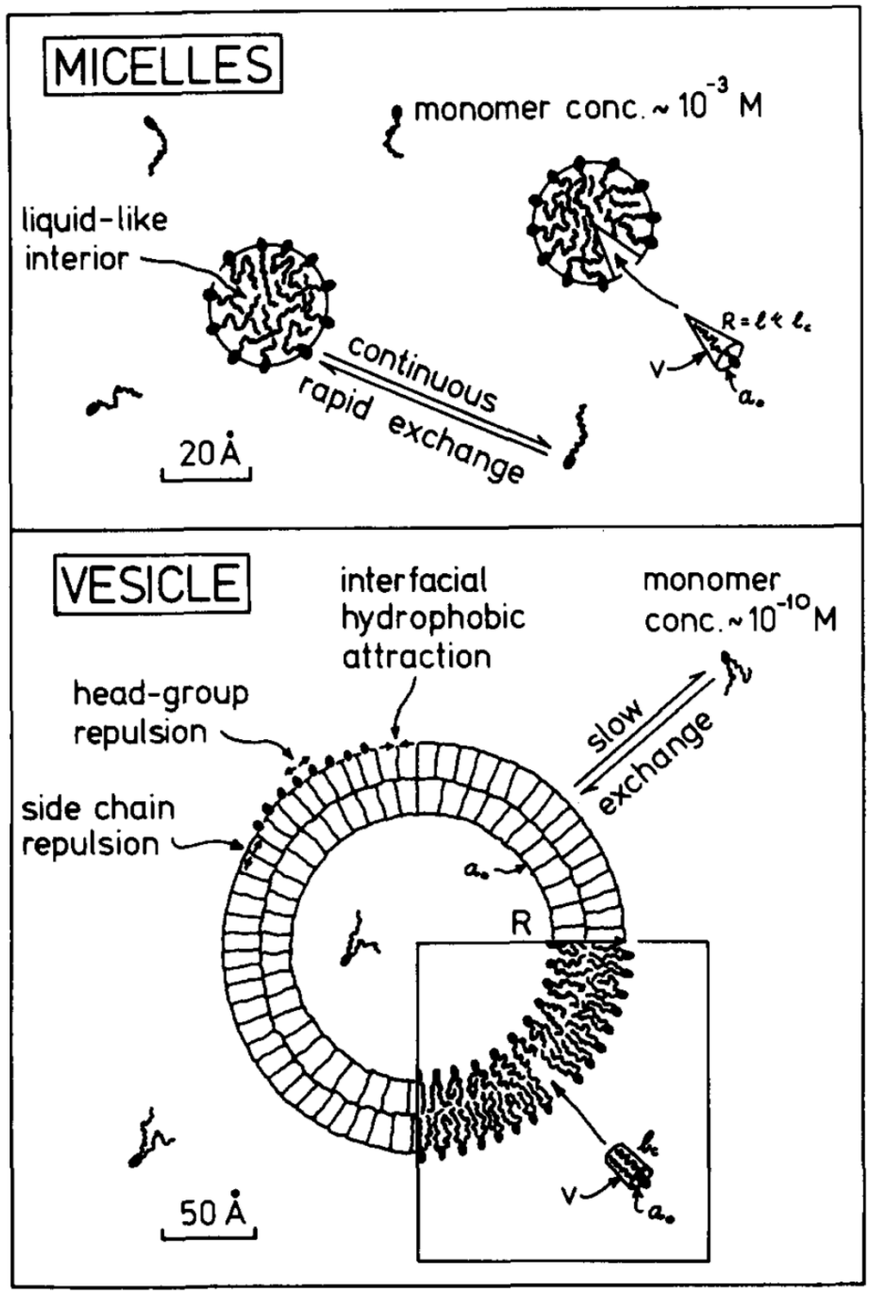
CHAPSO

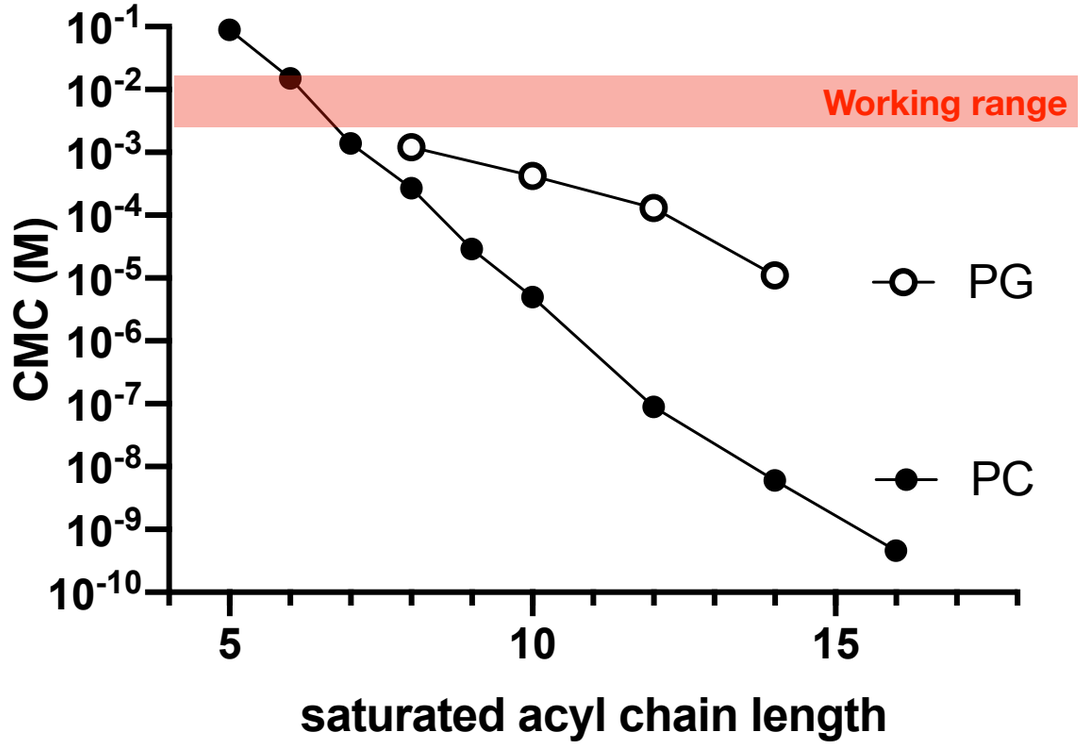




Prosser et al., 2006. **DOI:** 10.1021/bi060615u

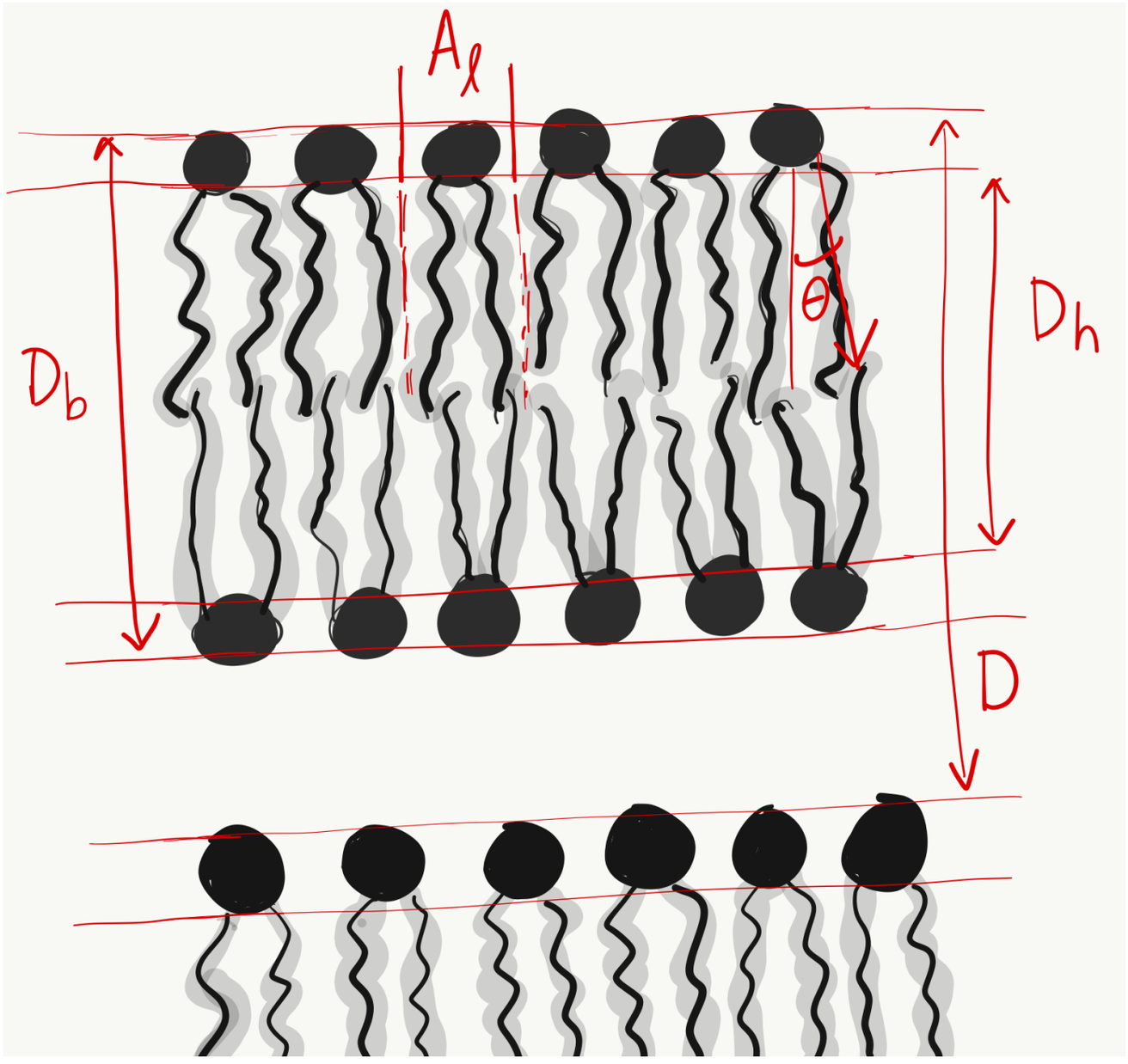
Self-assembly of lipid bilayers and liposomes





- Lipids, with two acyl chains, undergo the same type of self-assembly behavior, but the CMC values are now much lower.
- The exchange between free monomers and the lipid bilayer is slow
- Furthermore, liposomes are stable and do not fuse spontaneously

Bilayer & Lipid structural parameters

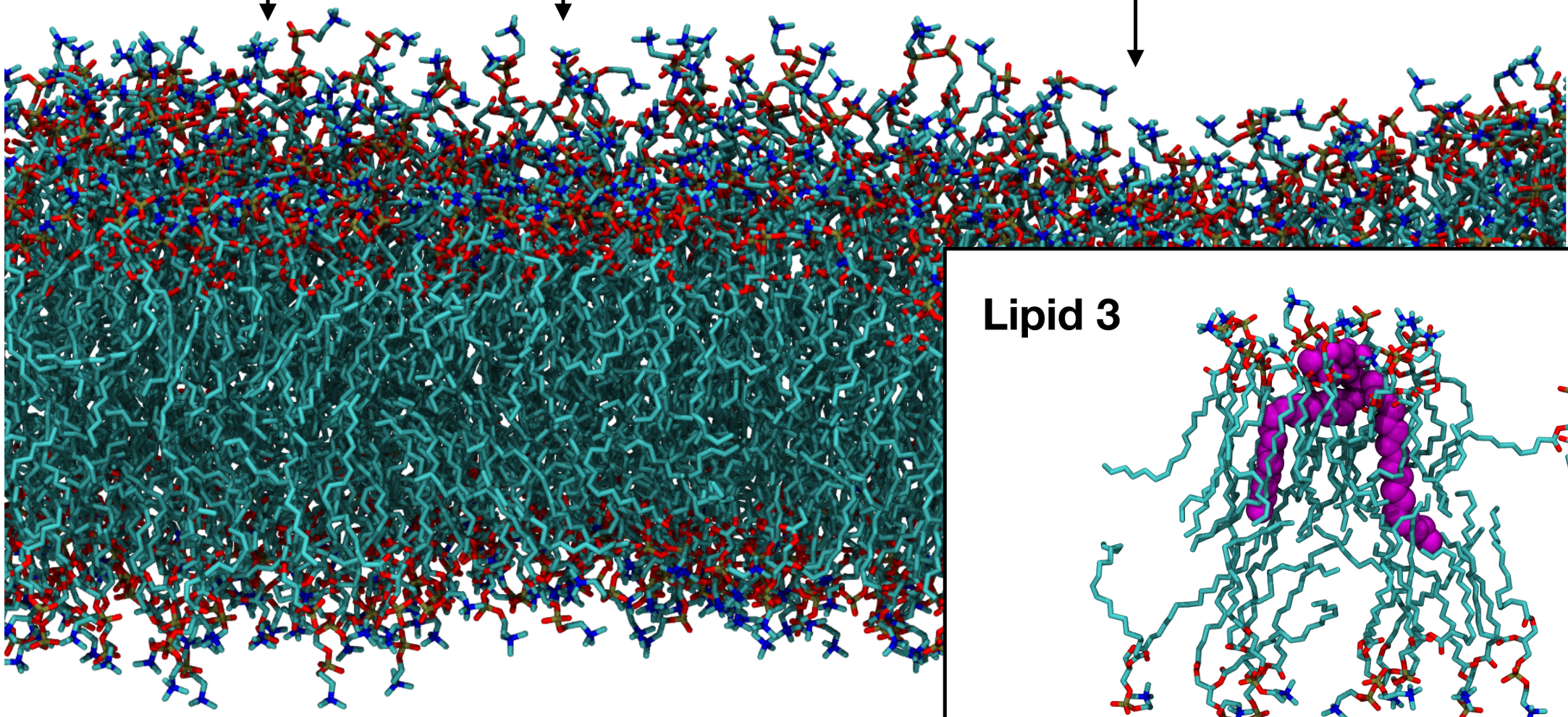


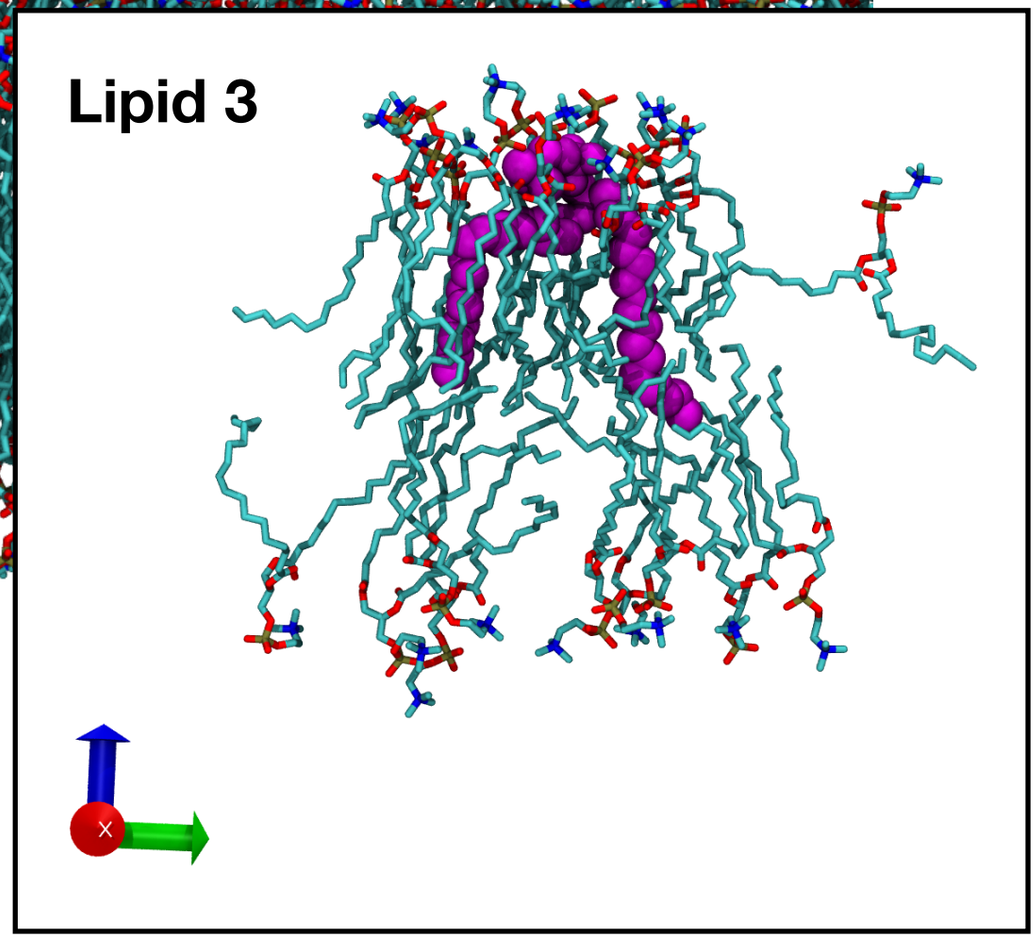
A_L - surface area of lipid
D - primary lamellar repeat spacing (multilamellar structures)
D_b - bilayer thickness
D_h - hydrophobic thickness
Θ - tilt angle of the hydrophobic tails

Lipid 1

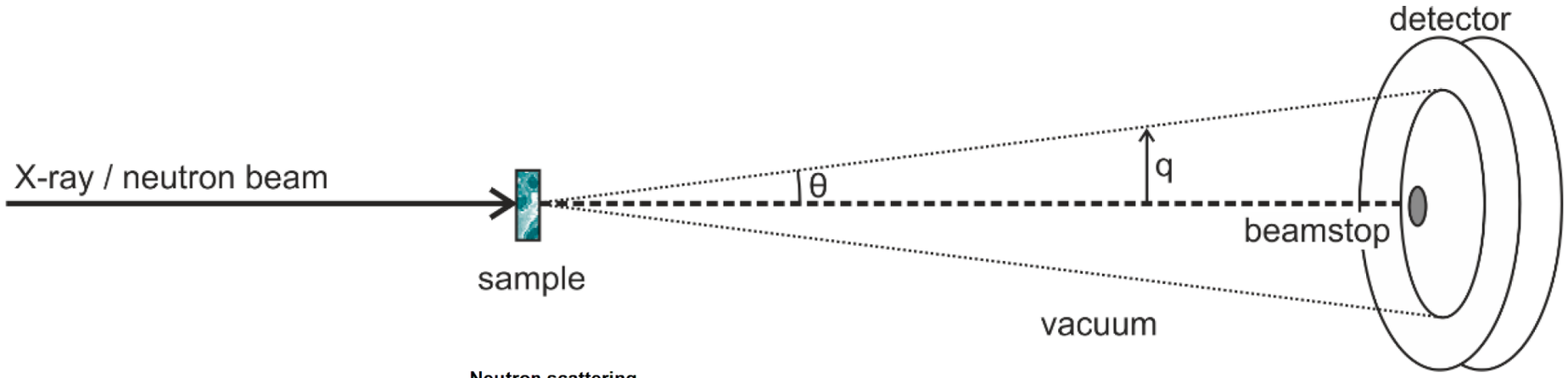
Lipid 3

Lipid 2





Small angle scattering to measure membrane structure



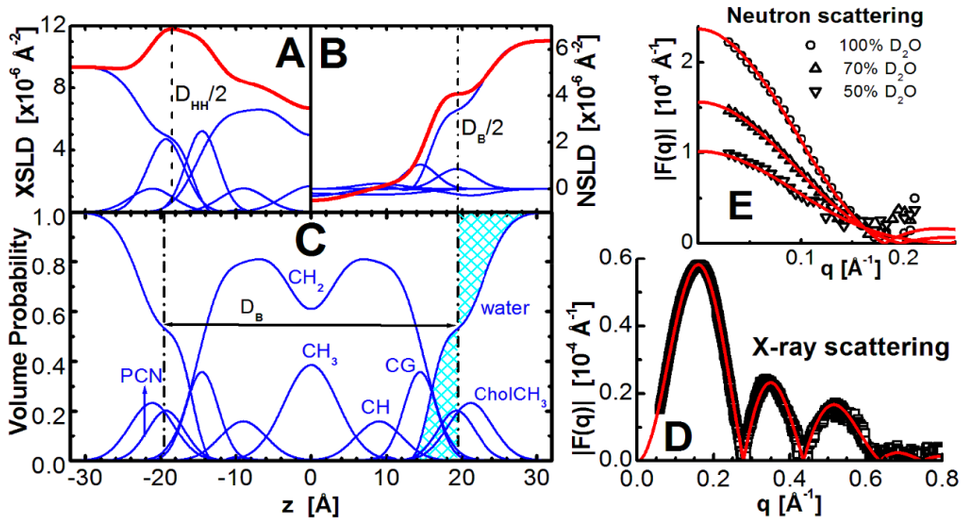


Figure 1. Illustration of lipid bilayer structure determination through the joint refinement of X-ray and neutron scattering data. The scattering density profile (SDP) representation of a bilayer in real space is shown on the left, where the top panels show X-ray scattering length density (XSLD) with amplitudes calculated from the number of electrons and electron radius (**A**), and neutron scattering length density (NSLD) based on neutron coherent scattering amplitudes (**B**) of lipid component distributions (see e.g., [33] for detailed description). The total scattering length densities are denoted by the thick red lines. Panel (**C**) shows volume probability distributions, where the total probability is equal to 1 at each point across the bilayer, and the location where the shaded areas are equal defines the Gibbs dividing surface between the lipid bilayer and the water phase (effectively D_B). Graphs on the right show the experimentally determined X-ray (**D**) and contrast varied neutron (**E**) scattering form factors (points), together with the best fits to the data (solid lines).

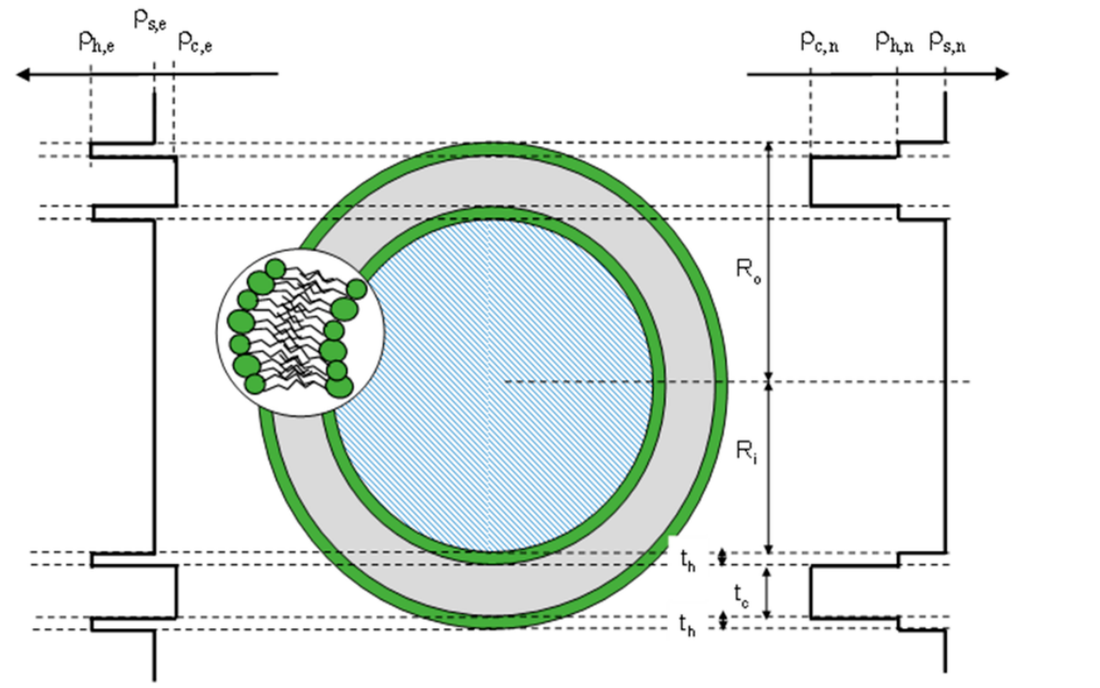
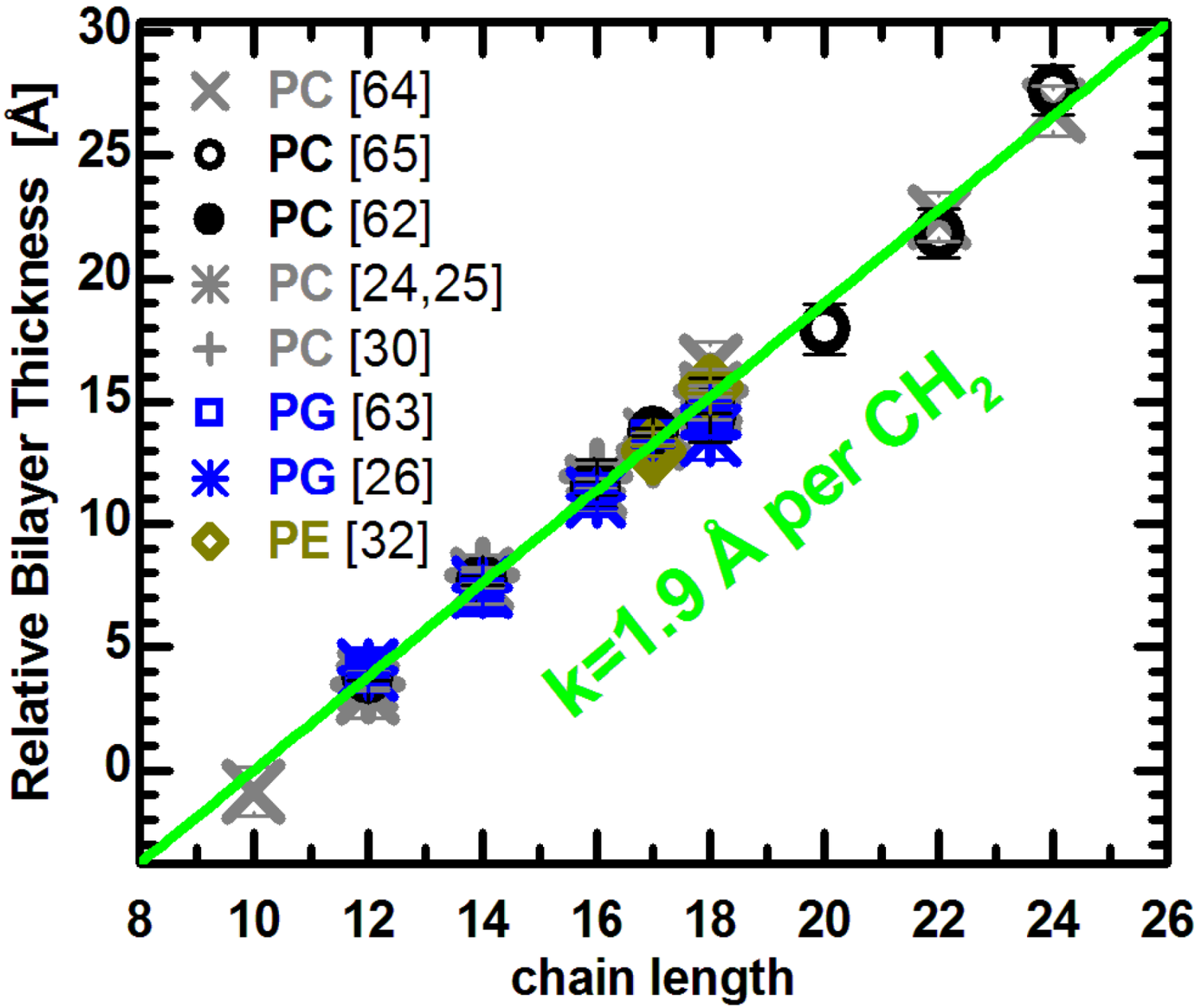


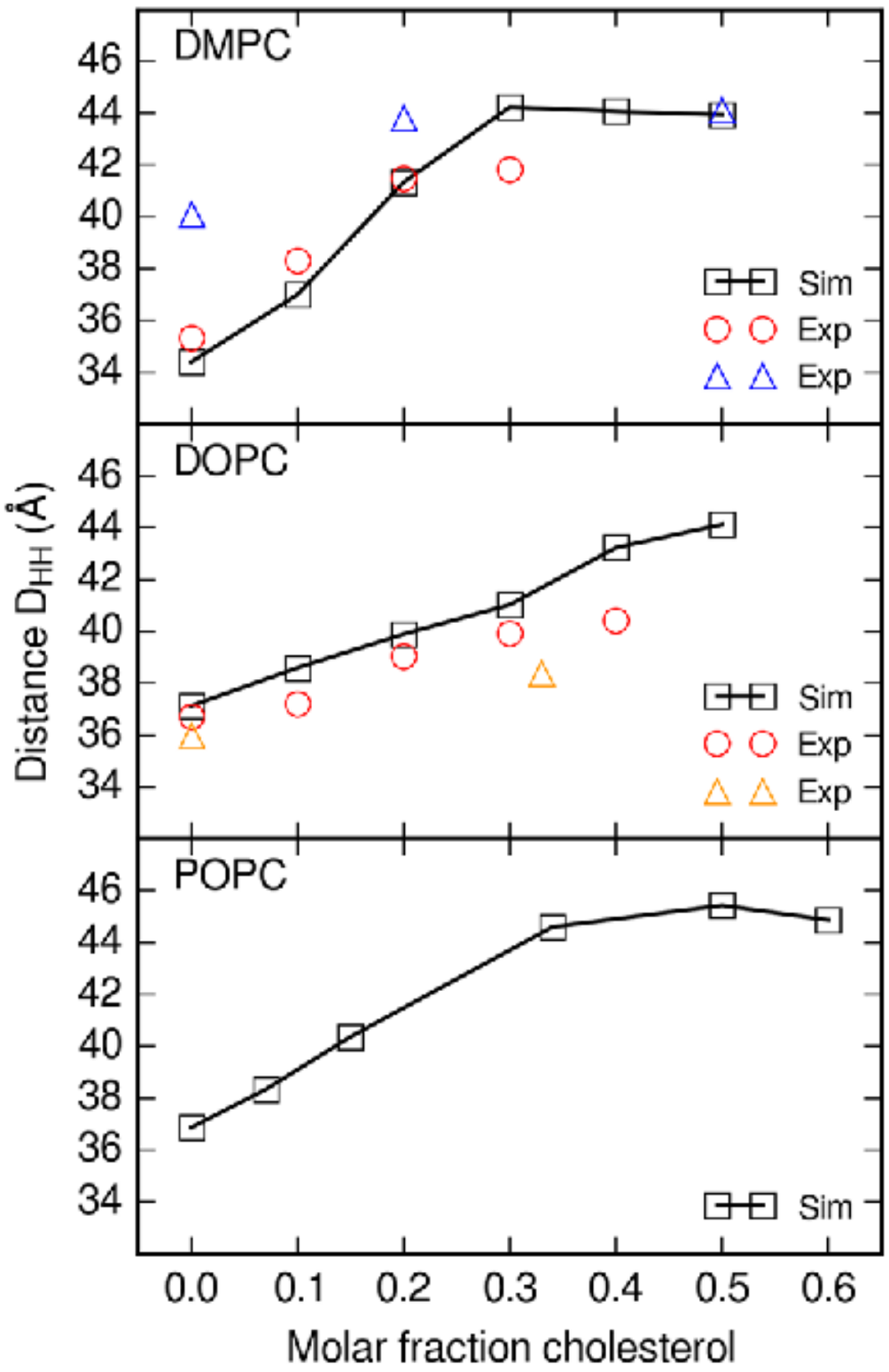
Figure 3. Comparison of the scattering length density profile of liposome for X-ray (**left**) and neutron (**right**). Adapted from [11].

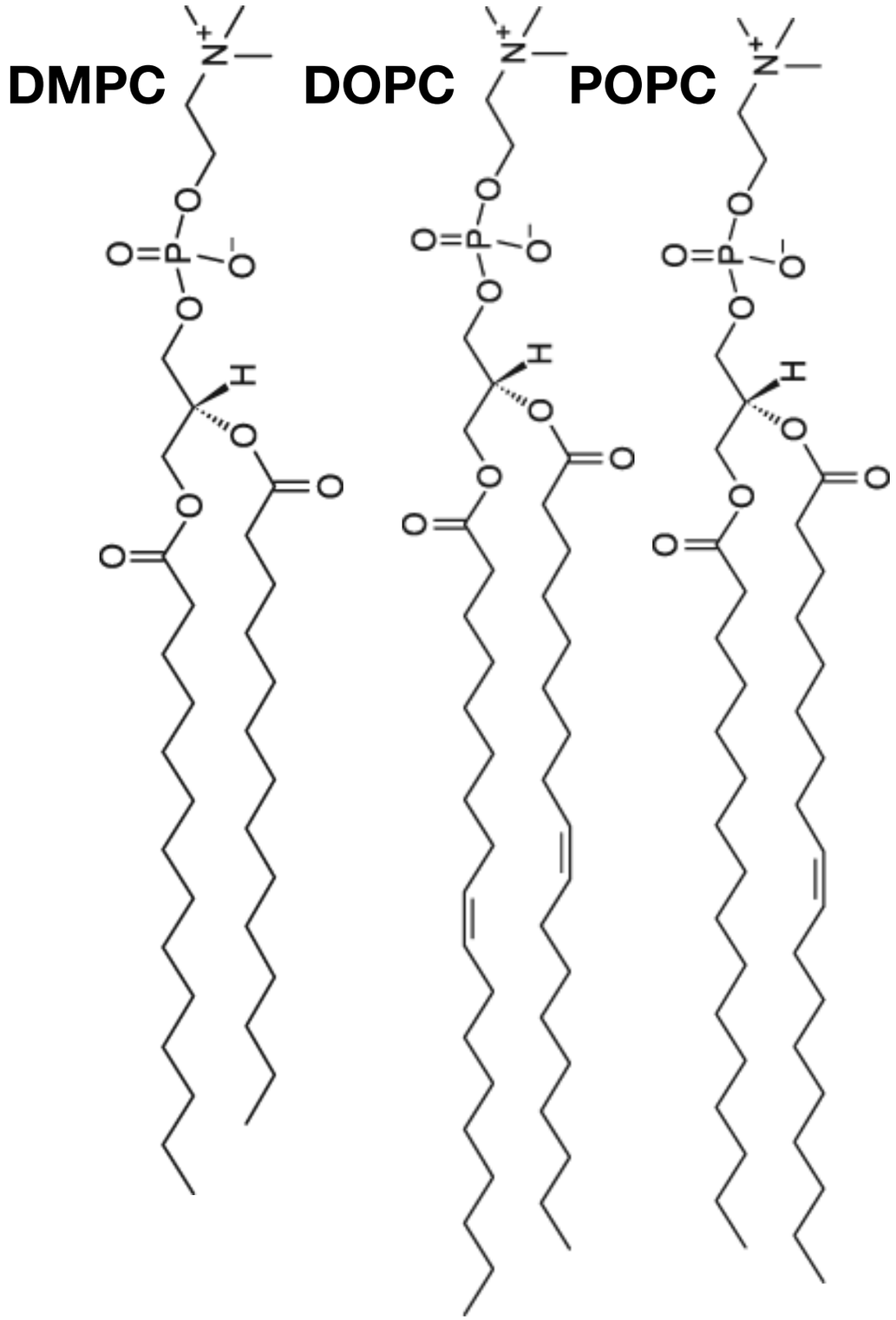
doi:10.3390/pharmaceutics8020010

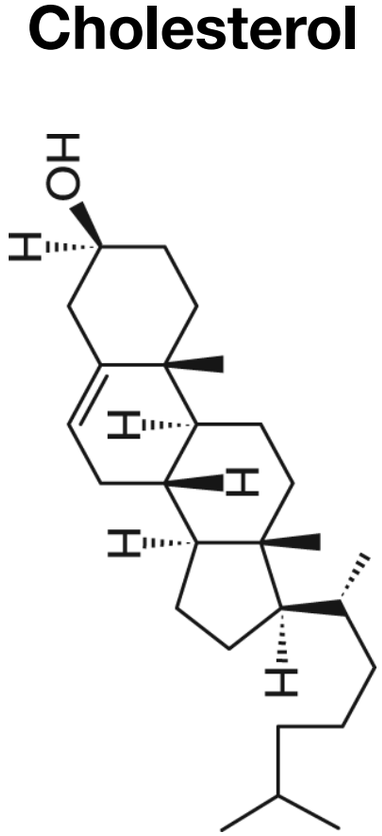
Bilayer thickness vs. acyl chain



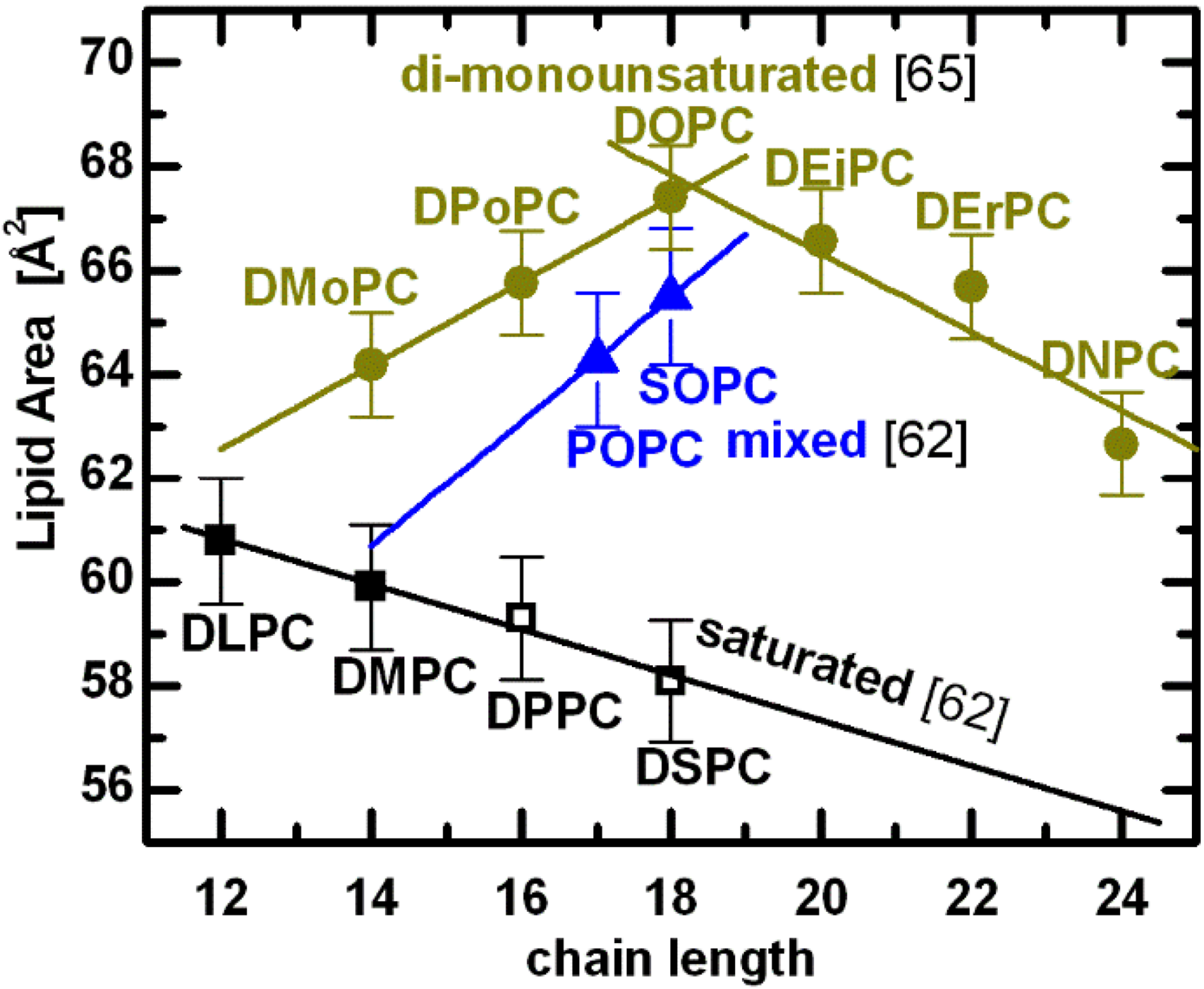
Hydrophobic thickness vs. cholesterol



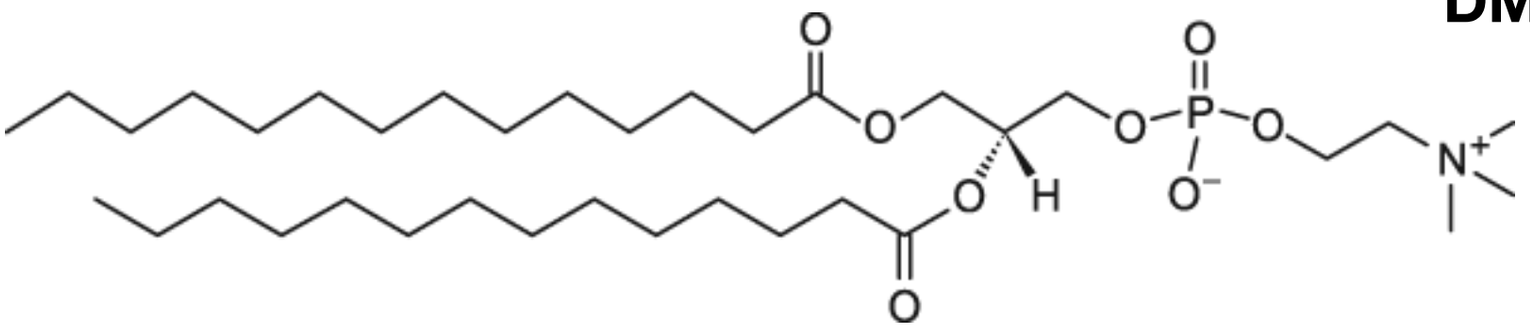




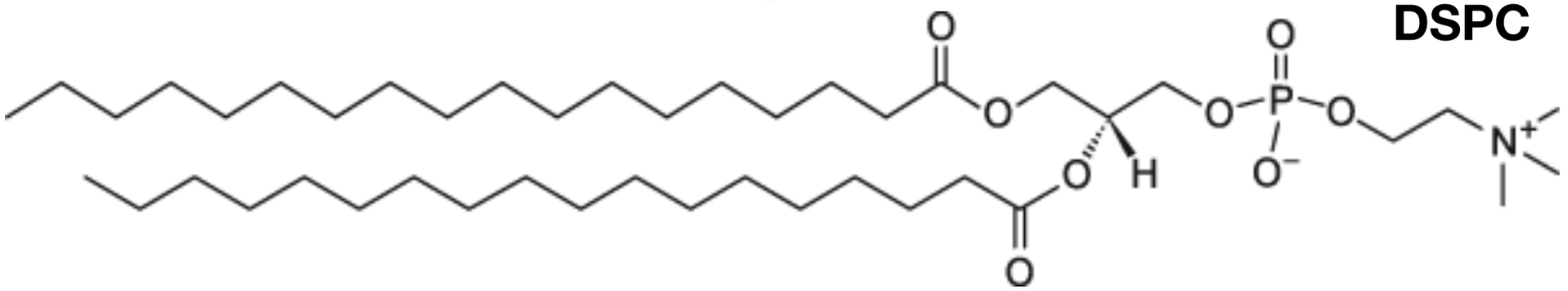
Bilayer thickness vs. chain modification



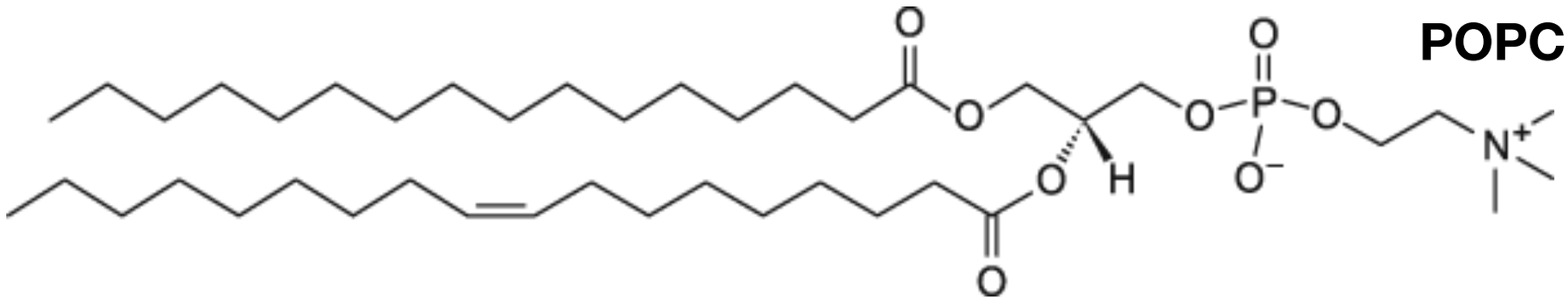
DMPC



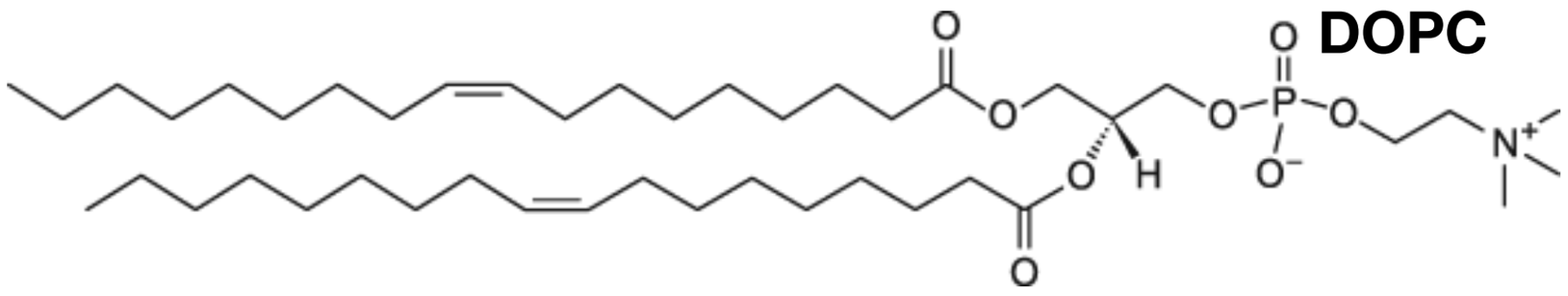
DSPC



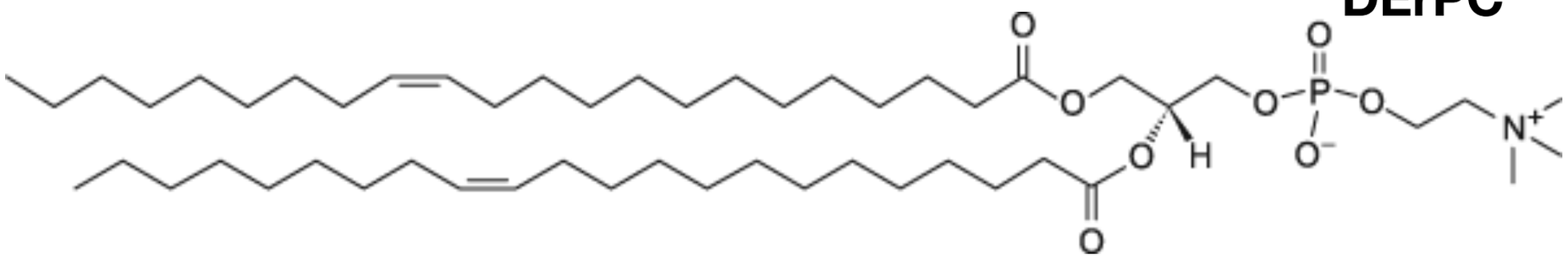
POPC



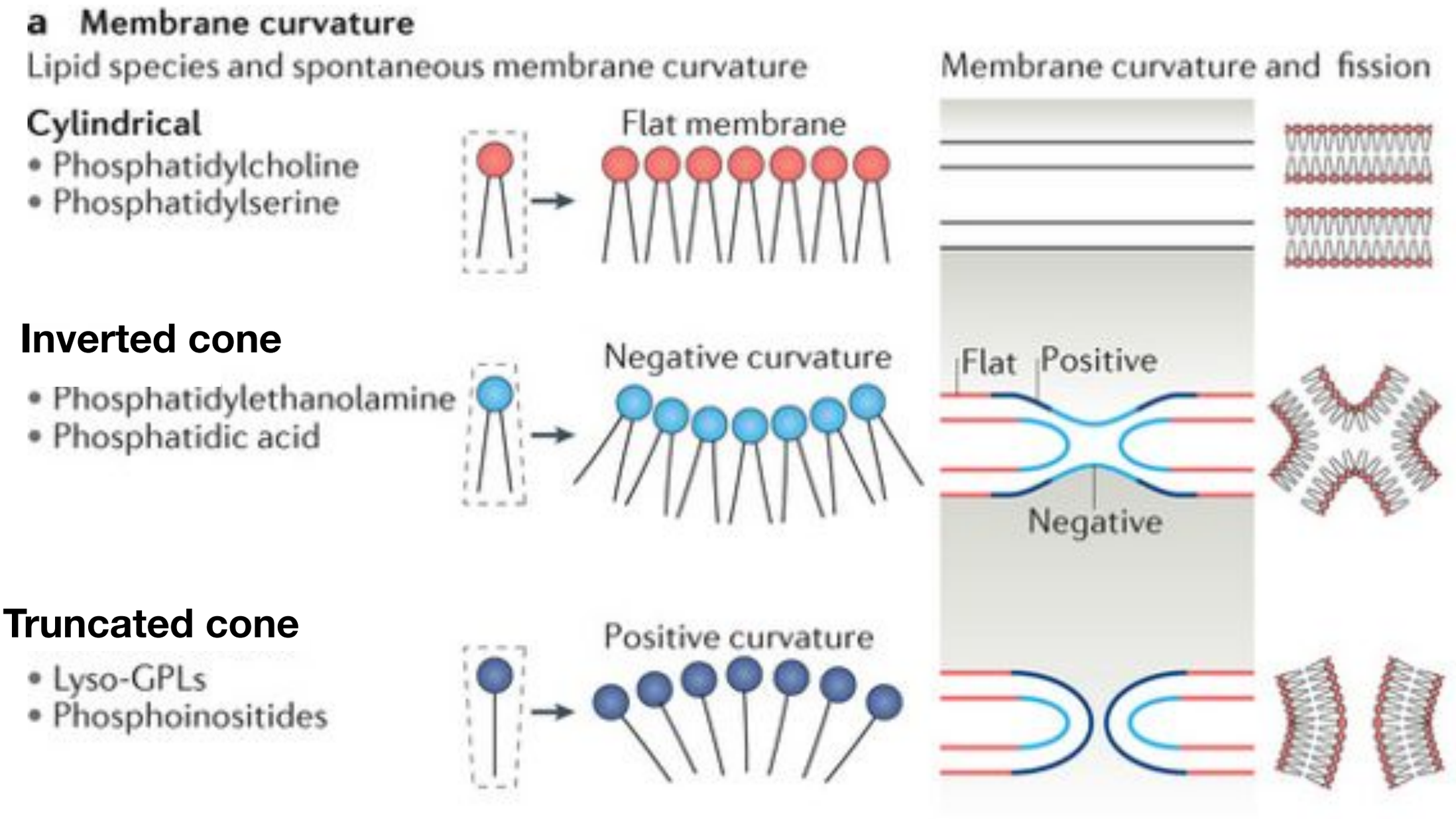
DOPC



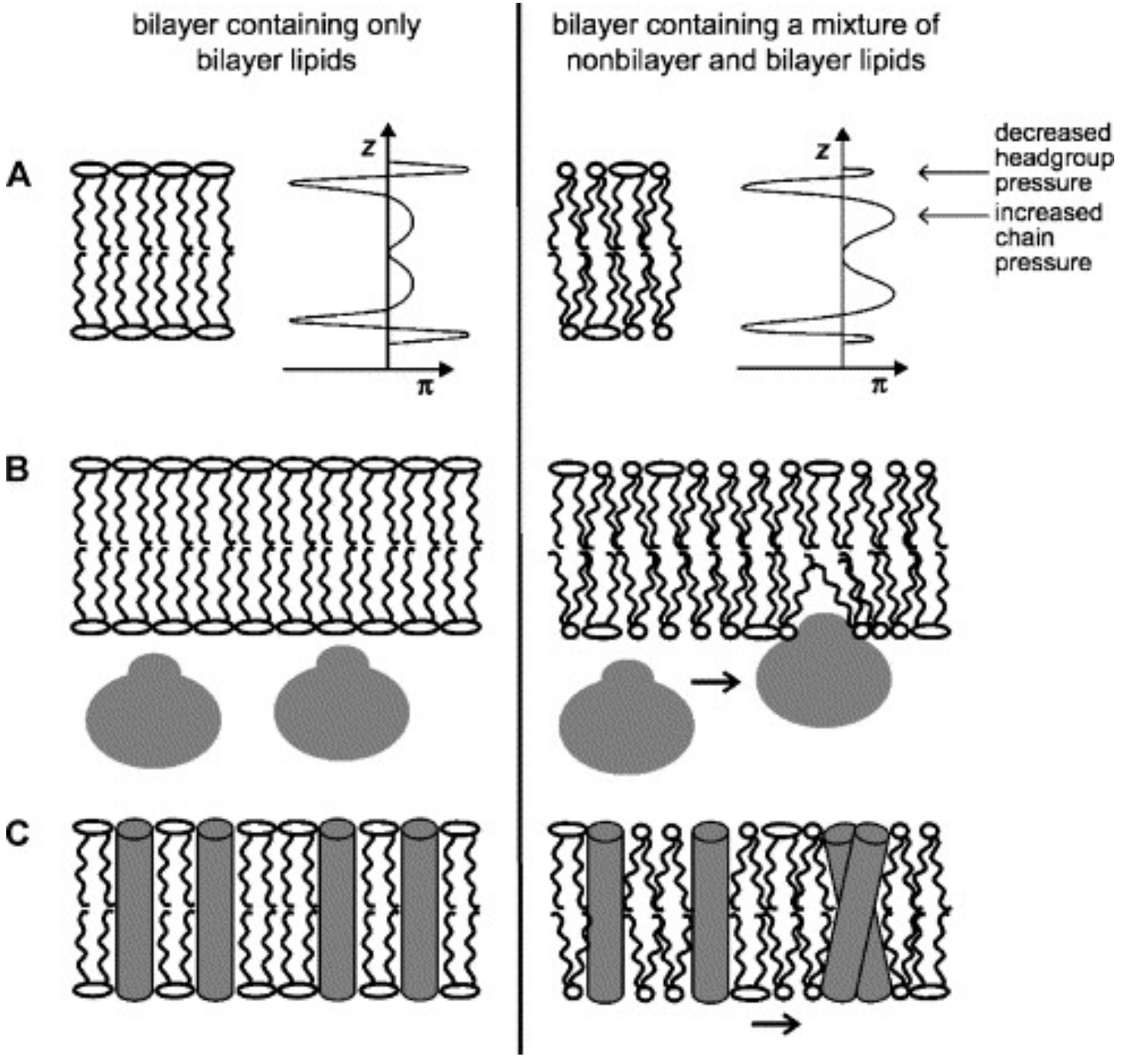
DErPC



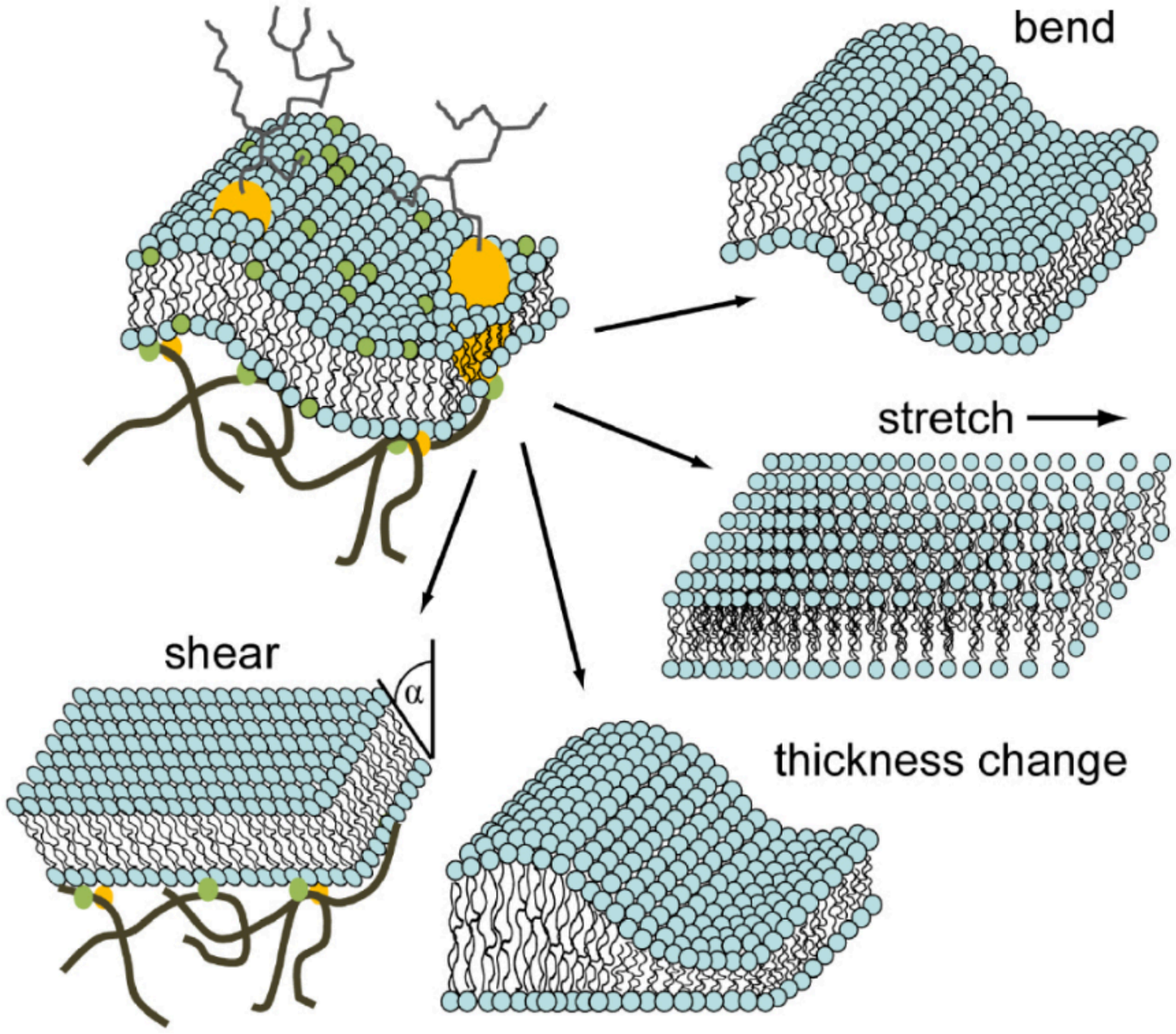
Lipid Bilayer Properties - Curvature



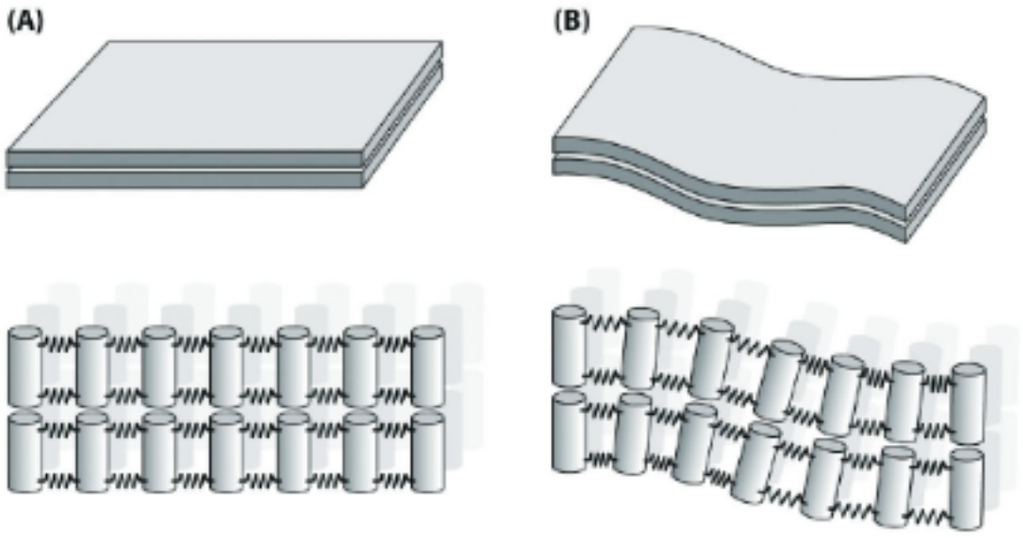
Lipid Bilayer Properties - lateral pressure



Material Properties of Lipid Bilayers



Energetic consequence of bending membranes



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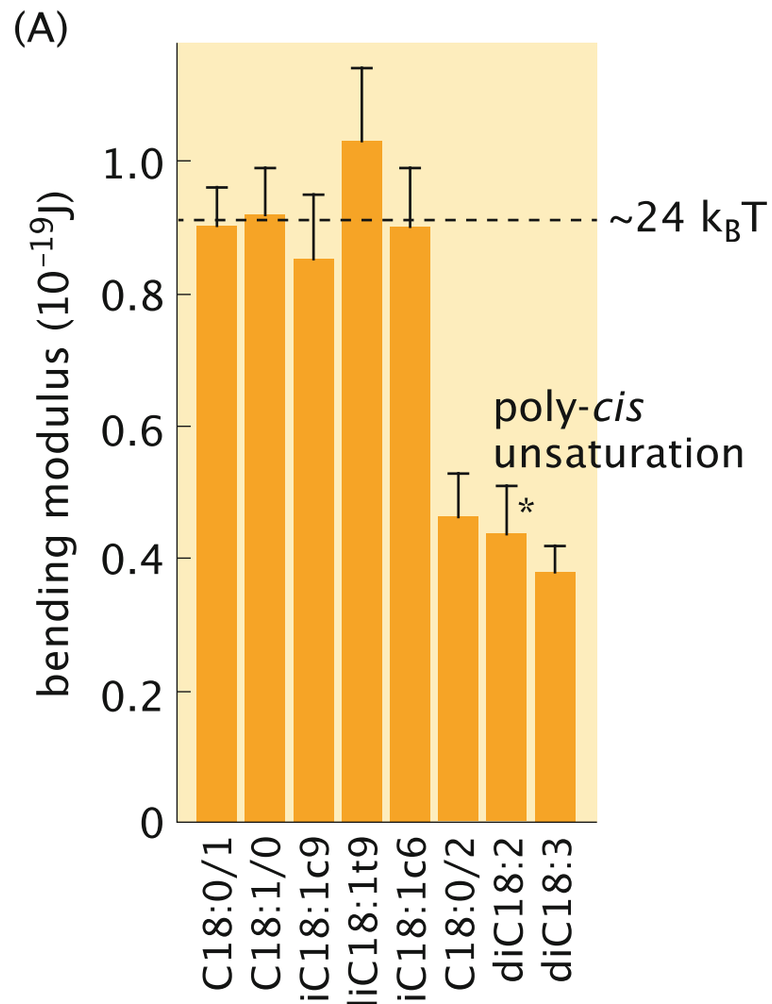


Helfrich-Canham-Evans Free Energy

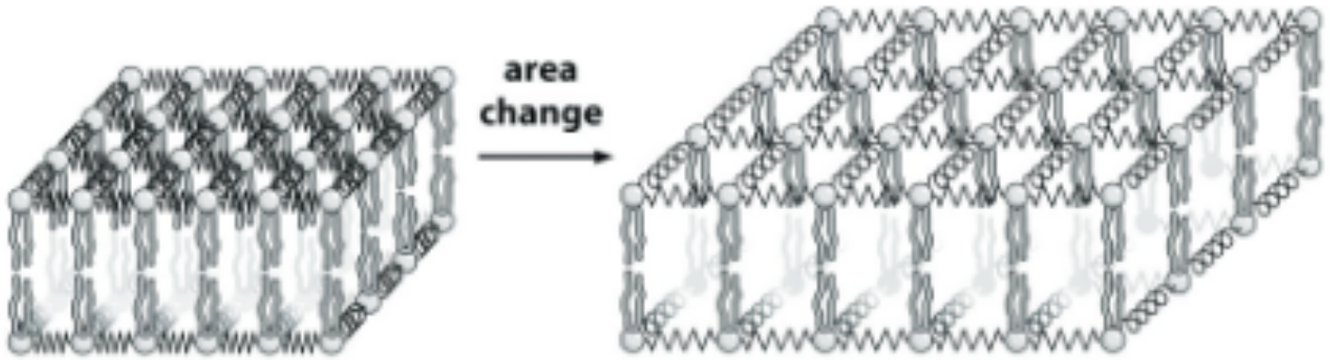
$$G_{bend}[h(x,y)] = \frac{K_b}{2}\int da[\kappa_1(x,y) + \kappa_2(x,y)]^2$$

$h(x,y) - membrane\ height\ at\ (x,y)\ [length, nm]$

$\kappa_{i,j}(x,y) = \frac{\partial^2 h}{\partial x_i \partial x_j} - principle\ curvature\ at\ (x,y)\ [1/length, 1/nm]$

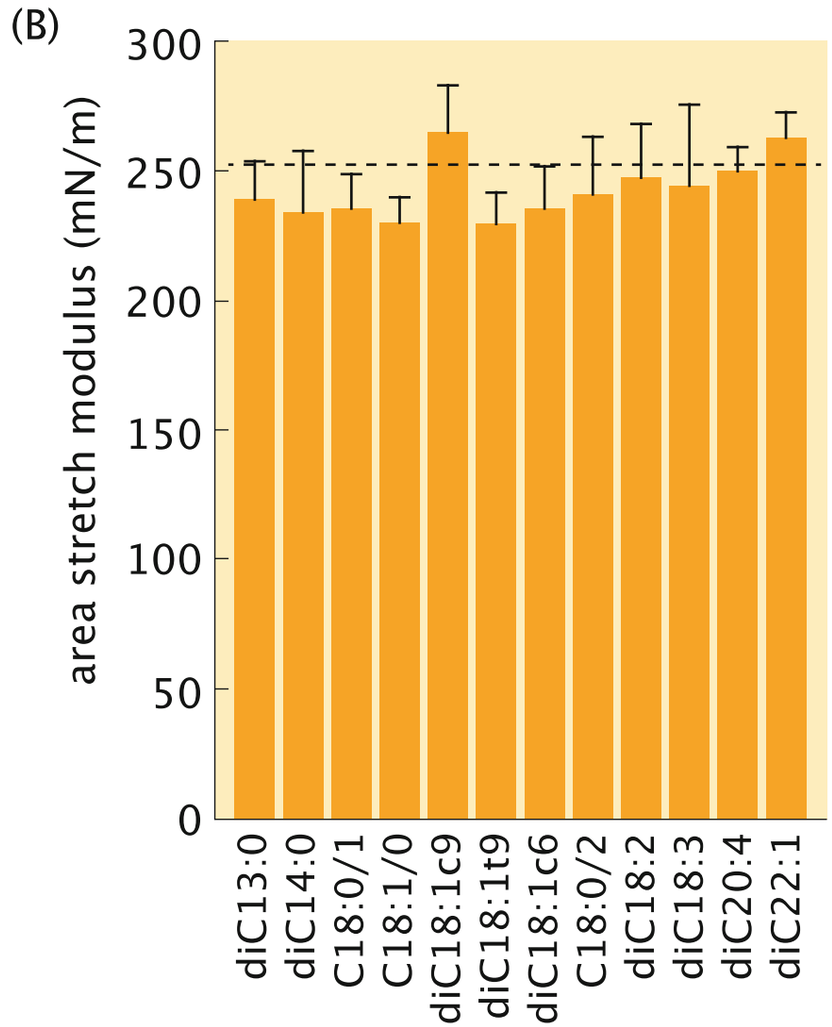
$K_b - \ bending\ modulus\ [energy, k_BT]$

Energetic consequence of stretching membranes

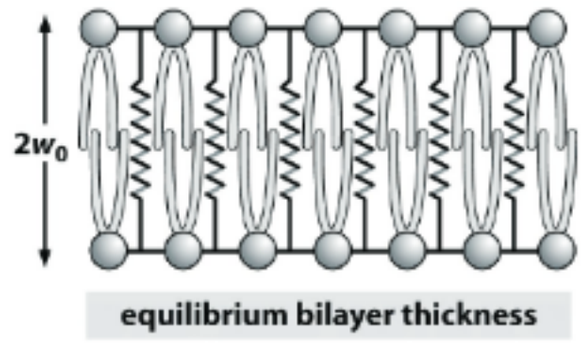


$$G_{stretch} = \frac{K_a}{2} \int da \left[\frac{\Delta a}{a_0}\right]^2$$

$\Delta a - change\ in\ area\ [area, nm^2]$
$a_0 - reference\ area\ [area, nm^2]$
$K_a - \ area - stretch\ modulus\ [energy/area, k_BT/nm^2]$



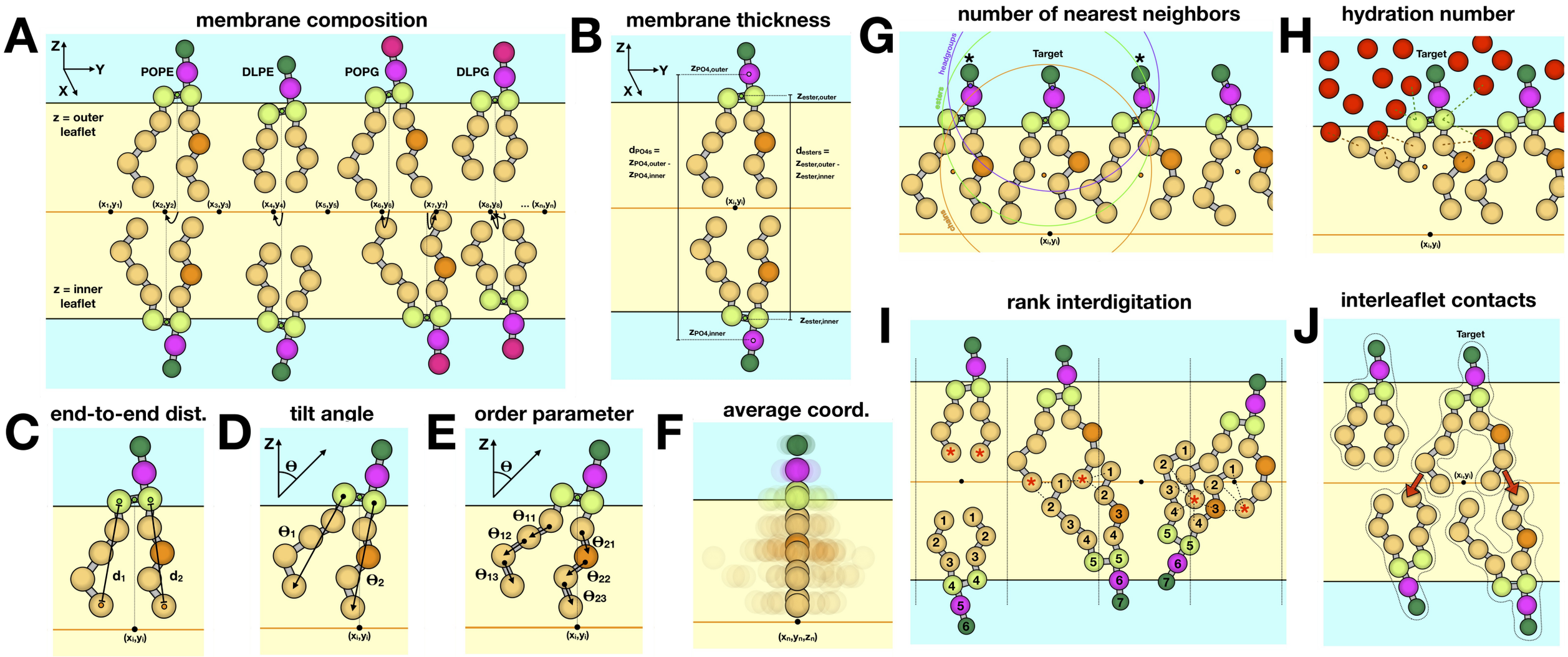
Energetic consequence of compressing membranes



$$G_{thickness}[w(x,y)] = \frac{K_t}{2}\int da\left[\frac{w(x,y)-w_0}{w_0}\right]^2$$

$w(x,y) - half - width\ of\ membrane\ [length, nm]$
$w_0 - half\ equilibrium\ width\ of\ membrane\ [length, nm]$
$K_t - \ stiffness\ modulus\ [energy/area, k_BT/nm^2]$

Molecular models are more complex



Rahul Chadda, Nathan Bernhardt, Elizabeth G Kelley, Susana CM Teixeira, Kacie Griffith, Alejandro Gil-Ley, Tuğba N Öztürk, Lauren E Hughes, Ana Forsythe, Venkatramanan Krishnamani, José D Faraldo-Gómez, Janice L Robertson (2021) Membrane transporter dimerization driven by differential lipid solvation energetics of dissociated and associated states eLife 10:e63288

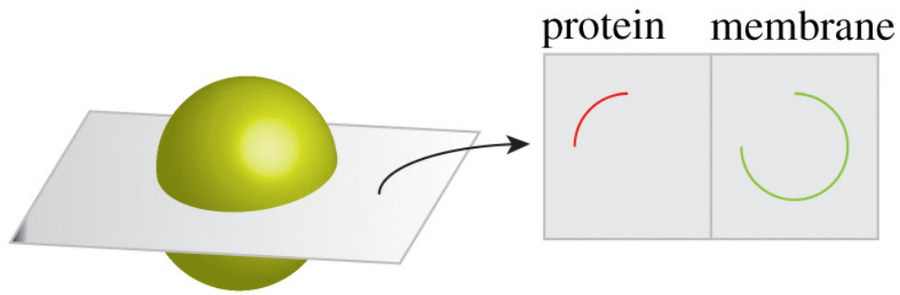
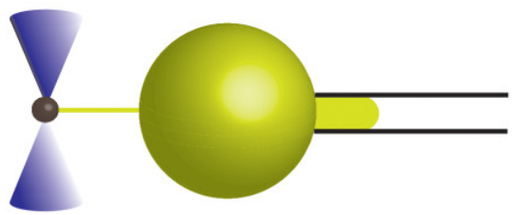
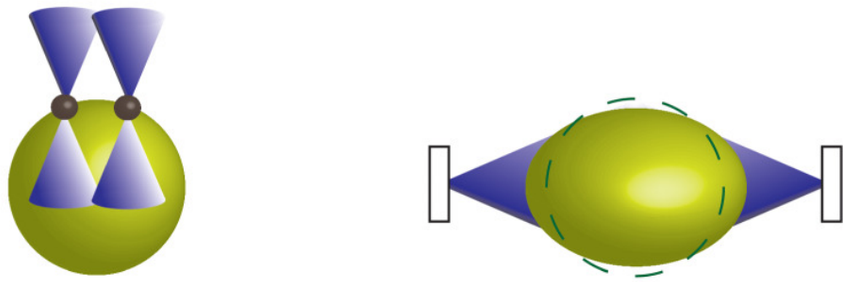
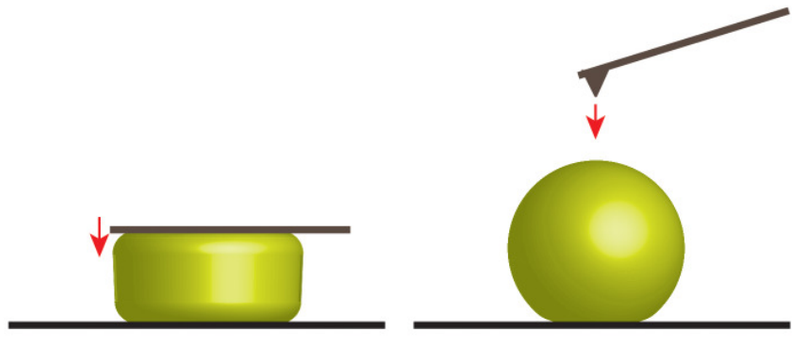
technique	schematic illustration	results [ref]
quantitative fluorescence microscopy		protein binding [102–104,106,107] lipid rafts [56,57]
micropipette aspiration combined with optical tweezers		membrane tension [92–94] bending rigidity [73]
optical trapping		bending rigidity [77–80]
atomic force microscopy		bending rigidity [82] membrane tension [83,84] area compressibility modulus [83,84]

Table 2 Membranes by the numbers

Membrane parameter	Range of parameter values	BNID
Lipid length	≈2.5–3.5 nm	See Table 1
Lipid area	≈1/4–3/4 nm^2	See Table 1
Number of lipids per cell (bacterium)	$\approx 2 \times 10^7$	100071
Bending rigidity	10–25 $k_B T$	105297
Area stretch modulus	200–250 mN/m (or ≈50 $k_B T/nm^2$)	112590, 112659
Membrane tension	$10^{-4} - 1\, k_B T/nm^2$	110849,112509, 112519
Rupture tension	1–2 $k_B T/nm^2$	112489, 110911
Membrane permeability (water)	10–50 μm/s	112488
Membrane capacitance	≈1 $\mu F/cm^2$	110759, 109244, 110802
Membrane resistance	0.1–1.5 $\times 10^9\ \Omega\, cm^2$	110802
Membrane potential	100 mV	109775, 107759
Diffusion constant (lipid)	≈1 $\mu m^2/s$	112471, 112472
Diffusion constant (membrane protein)	≈0.02–0.2 $\mu m^2/s$	107986

A summary of the key numbers about membranes discussed throughout the chapter for easy reference. Numbers reported are "typical" values and should be used as a rule of thumb. For a more detailed description of parameter values, the reader should use the Bionumbers database through the relevant BNID. Also see Box 1 of [14]

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